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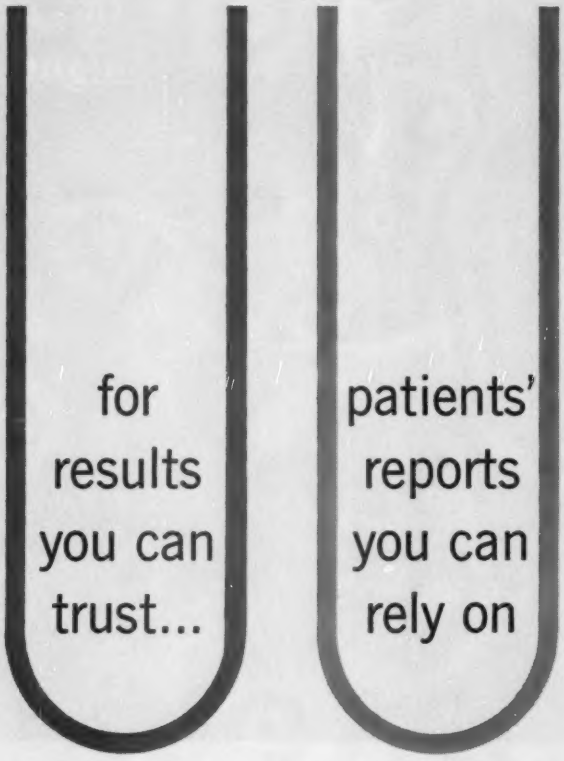

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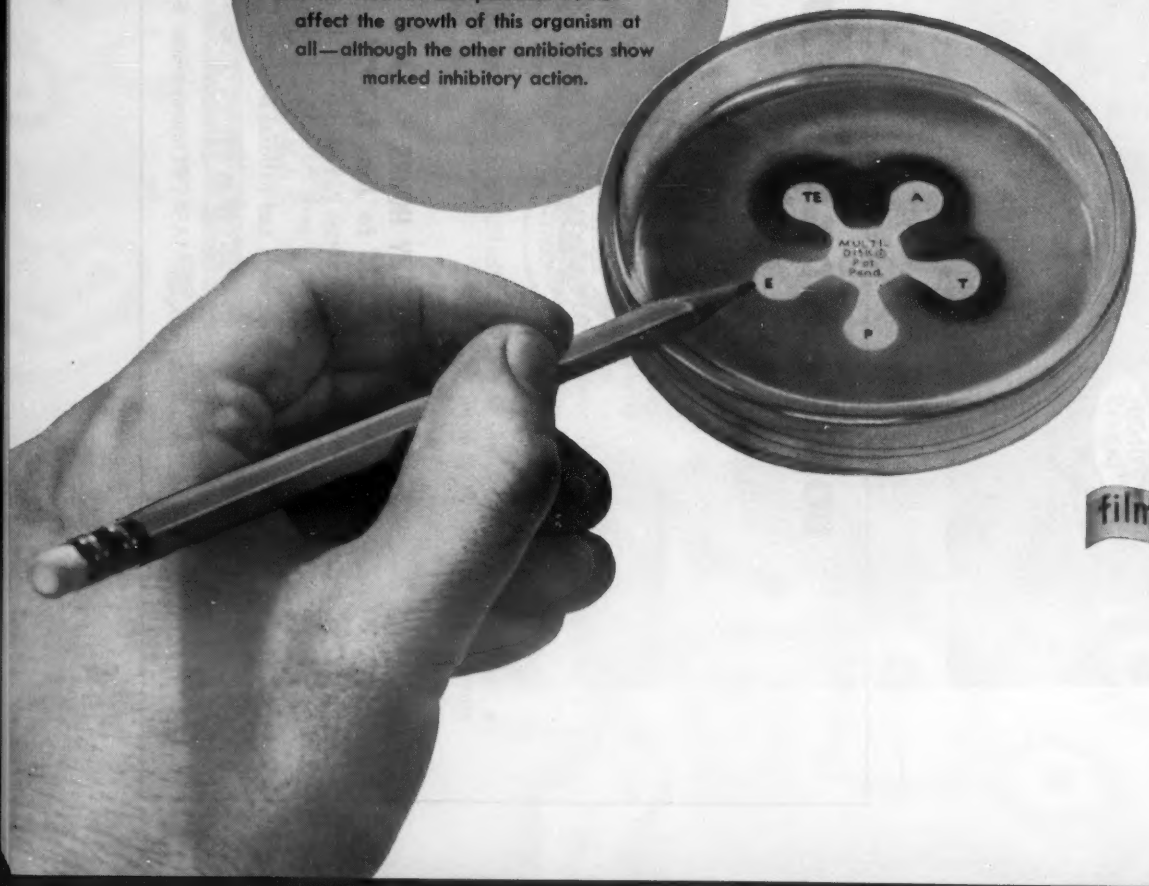

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1. Lewis, L., et al.: Ann. Int. Med. 39: 116, 1953.
2. Spies, T. D., et al.: GP 12: 73, 1955.

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Genito-urinary disorders	23	74%
Postoperative nausea and vomiting	15	90%
Nausea and vomiting of pregnancy	7	71%
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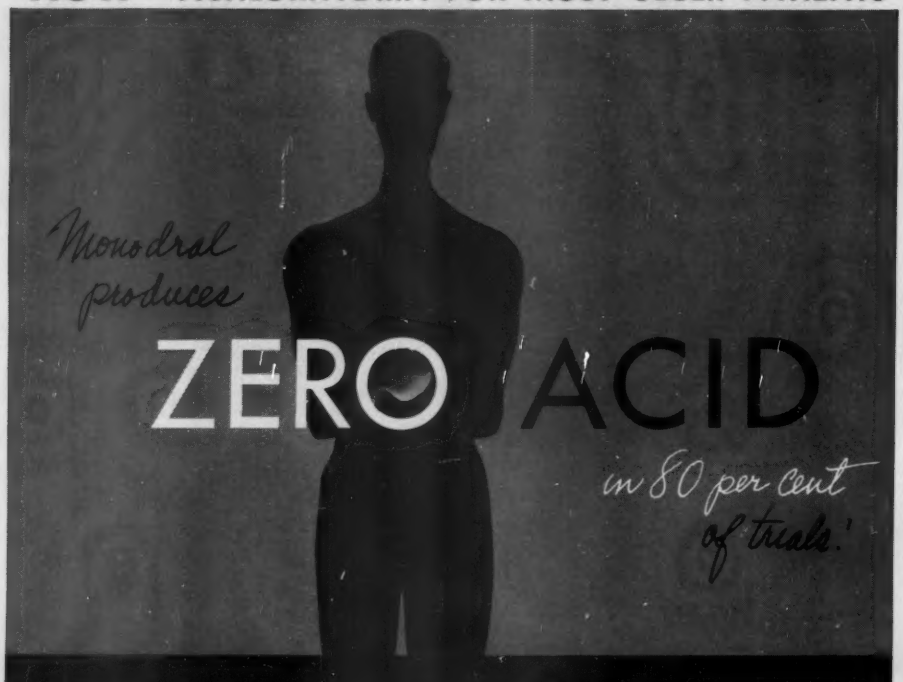

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Volume 253 OCTOBER 20, 1955 Number 16

IMPROVED VALVULOPLASTY FOR MITRAL STENOSIS*

With a Discussion of Multivalvular Disease

DWIGHT E. HARKEN, M.D.,† AND HARRISON BLACK, M.D.‡

BOSTON

THE surgical correction of mitral stenosis is now widely accepted and utilized. Before operation it is possible to assess risk accurately. This ranges in well defined classes from less than 1 per cent to more than 33 per cent.§

Precise knowledge of the surgical risk and better appreciation of mortality and morbidity under good medical treatment clarify the proper time and place for surgical intervention.

Much has been written about the mortality of operation and late results in terms of survival. Mortality and morbidity have been progressively reduced by better preoperative and postoperative care.[1] It is of fundamental importance to carry out objective long-term studies such as those of Ellis and Harken[2] to determine the degree of rehabilitation possible in the various clinical groups. The proper selection of patients for operation also bears directly on the results.

There still remains, however, a fundamental factor that influences all others — namely, *the quality of the operative correction of the valvular stenosis.* Discussion of this cardinal matter has heretofore been neglected for three reasons. In the first place, until recent years, it has been considered a notable *tour de force* for a surgeon to thrust his finger into the heart, through the stenotic mitral orifice, with moderate hemostasis and survival in some cases. Secondly, variations in the pathologic patterns have presented technical problems of varying complexity. Thirdly, the surgeon's concept of what he has accomplished at operation is conditioned by the pathologic pattern encountered and his skill and experience in dealing with it.

If the degree of rehabilitation and the quality of results are to continue to improve, frank discussion and mutual understanding are essential among those responsible for the patients' care. Some technical considerations are reviewed here that influence not only the *mortality* but also the *quality* of the surgery. Incidentally, the significance of *valvuloplasty* as opposed to simple *commissural opening* is emphasized. It is hoped that the inadequacy and transient value of *dilatation* will become apparent. Operative technics that safeguard against the *production* of mitral incompetence are described. The "recurrence" of mitral stenosis is discussed.

The literature still contains references to "dilatation of the mitral valve" and to "commissurotomy" and even statements that indicate that some surgeons are satisfied with opening the stenotic mitral orifice to 2.0 to 2.5 square cm. It is hoped that these are merely loose expressions and not correlated with the actual surgical procedure. Extensive experience has clearly demonstrated that "dilatation" is commonly of only temporary benefit, that "commissurotomy" does not correct secondary stenosis (below the leaflet level) and that a valve orifice of 2.0 square cm. in area may actually represent hemodynamically significant stenosis in many patients.

SURGICAL EXPOSURE OF THE HEART

The lateral thoracotomy incision is preferable to any of the compromises (Fig. 1). It has been urged that the anterior approach is "better for the patient" and "simpler for the surgeon." Initially, we employed an anterolateral incision in the dorsal decubitus position and were convinced that the poor-risk

*From the Department of Surgery, Peter Bent Brigham Hospital and Harvard Medical School.

Supported in part by Grant No. 442 from the National Heart Institute, United States Public Health Service.

†Associate clinical professor of surgery, Harvard Medical School; surgeon, Peter Bent Brigham and Malden Hospitals; chief of thoracic surgery, Mount Auburn Hospital.

‡Instructor in surgery, Harvard Medical School; associate in surgery, Peter Bent Brigham Hospital.

§Recent experience with valvuloplasty for pure mitral stenosis indicates that the mortality for Groups 2 and 3 is less than 1 per cent (1 death in the last 220 consecutive cases). Deaths are almost exclusively from embolization. Thus, the risk in this group is virtually limited to patients over thirty-five years of age, those in atrial fibrillation or those who have calcification of the mitral valve. In Group 4 (those in chronic congestive heart failure or over the age of fifty), two subgroups can be identified. In Group 4a, those in chronic, irreversible failure who are not getting worse under therapy, the risk of operation is approximately 15 per cent. In Group 4b, those whose failure is increasing despite meticulous medical care in the hospital, the mortality (early and late) approaches 33 per cent. To put it another way, the salvage rate of these apparently dying patients may be only 67 per cent.

patient tolerated this better than the lateral position. However, with improved technics of anesthesia, involving principally minimal amounts of agent and mechanically assisted respiration,[1] it has become possible to manage the patients who are the most desperate risks in the lateral position. For the past three years we have used the standard hemithoracic lateral thoracotomy because of the vastly improved exposure of the base of the atrial appendage. The opposing hemostatic purse-string sutures are thus more easily placed over a broad area of atrium at the base of the appendage. This exposure has virtually eliminated difficulty in managing atrial tears and other technical problems. There have been no deaths related to control of hemorrhage from the atrial appendage for hundreds of operations.

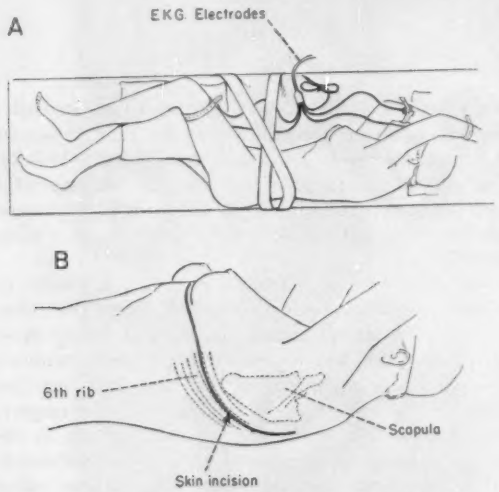

FIGURE 1. *Technic of Surgical Exposure of the Heart.*
A= *lateral decubitus incision, with electrocardiographic leads in place.*
B= *parascapular incision terminating anteriorly just below the breast.*

Obliterated Appendage

The lateral exposure makes it possible to expose the atrium for cardiotomy even though there may be no appendage because of atrophy, thrombosis, calcification or previous operation. We no longer recognize an "inoperable appendage." In patients over fifty, and in those with organized clot in the left atrium, almost complete obliteration of the lumen of the appendage is frequently found. The proper management of this problem entails the use of three concentric purse-string sutures placed widely about the base of the appendage. A stab incision is carried through the contained area. This is enlarged with a Kelly clamp followed by the finger, which cautiously dilates the opening. If the purse-string sutures are placed widely enough on the atrial wall, control of the hemorrhage that follows removal of the finger after valvuloplasty presents no significant problem. Similarly, when reoperation is necessary because of previous inadequate operation for mitral stenosis, the appendage may have been excised or obliterated by sutures. Furthermore, adhesions between the pulmonary veins and the atrium reduce the presenting area of atrial wall. In such cases it is necessary to separate the superior pulmonary vein from the left atrial wall and the base of the appendage from the pulmonary artery by blunt dissection. One then has the choice of going through the base of the obliterated appendage or of placing purse-string sutures on the flat surface of the wall of the atrium itself and making a stab incision within the area circumscribed by the sutures.

Formerly, we used the superior pulmonary vein for entry in reoperation or when the appendage was obliterated. Further experience indicates that incision directly through the wall of the atrium is safer and places the cardiotomy closer to the mitral valve. A small valvulotome (No. 9 breadknife, described below) has almost invariably been necessary in the reoperations but its insertion has presented no technical problems. Glenn et al.[3] have described a rubber diverticulum that can be sutured to the wall of the atrium as a solution for this problem of the obliterated appendage. This ingenious technical principle will no doubt be useful, but we have not yet found it necessary.

Tears of the Atrial Wall

The atrial wall may be torn during finger insertion or may be cut with the valvulotome proximal to the purse-string sutures. Such accidents are terrifying and may even result in fatal hemorrhage if the surgeon does not proceed deliberately. Bleeding can invariably be controlled if the surgeon tightens the purse-string sutures on his intracardiac finger and occludes the laceration from within. Either the surgeon or his assistant can then carefully place additional sutures proximal to or in the tear in a dry field. Obviously, if the finger is removed before this is done, there may be massive hemorrhage and great difficulty in visualizing the laceration. On rare occasions, when suture control has been incomplete, Gelfoam sponges have been packed between the pulmonary artery and the wall of the atrium. If these are held in place until they adhere they may control the low pressure leak satisfactorily. Gelfoam sponges can be held firmly against other portions of the atrial wall by tight pericardial suturing.

At the time of these emergencies the great temptation is to grasp hurriedly and blindly with a clamp in the bottom of a torrent of blood. This can further lacerate the atrium or damage the left coronary artery in the atrioventricular groove. Orderly occlusion from within, if the finger is inside the heart, or digital compression from without, if the finger has been re-

moved, will control hemorrhage and allow deliberate, precise management of the laceration.

As we have trained many competent groups of surgeons in these technics we have become aware of the need for special emphasis on what at first thought seems a superfluous warning. It will seem ludicrous to the inexperienced and insulting to the experienced. It is neither; it is important. This point is that one should *look at the cardiotomy site and operating finger during the intracardiac manipulation.* For some reason — perhaps conditioning by rectal or pelvic examination or perhaps an alarm reaction that prompts the surgeon to face away from danger — there is a tendency nothing short of *compulsion to look away from the operative field* at the time the finger is in the heart. During such blind periods accidents, either absurd or tragic, may occur: the finger may slip out of the heart; the atrium may be torn without the knowledge of those operating; or cardiac arrhythmia may develop. The sound principle of watching what one is doing needs no defense but strict adherence to this principle requires some special mental discipline.

Embolus

Migration of clot from the left atrium or calcium emboli from the mitral valve now constitute the chief source of morbidity and mortality in the surgery of mitral stenosis, particularly in Group 3 patients. It is doubtful if this threat will ever be entirely eliminated. However, obstruction of the circulation to the brain during the dangerous portions of intracardiac manipulation has a reasonable place in the reduction of cerebral emboli. Our current practice is to isolate the right innominate, left common carotid and left subclavian arteries and pass rubber-dam drains about them (Fig. 2 *A* and *B*). During the manipulation of the atrial appendage, insertion of the finger into the atrium and fracture of calcified valves the circulation to the brain is obstructed by traction on the rubber dams. This obstruction is maintained for a period of at least thirty to forty-five seconds *after* any maneuver that might dislodge particles into the blood stream, since the passage of such particles from atrium to ventricle and thence up the aorta may take an appreciable period.

The subclavian artery has been occluded in addition to the others since the occurrence of one fatal calcific embolus to the basilar artery via the left vertebral artery, when only the innominate and left common carotid arteries had been occluded during manipulation of the valve. An alternate method of obstruction of these vessels is to place a bulldog clamp on the left subclavian artery for the duration of the intracardiac maneuver and use fast-action Blalock clamps for brief obstruction of the innominate and left common carotid arteries.

Experience has shown that it is wise to limit the duration of such obstruction if possible to one minute and never to exceed a minute and a half. If further dangerous manipulation is necessary the cerebral circulation can again be obstructed after a rest period of approximately two minutes during which blood is allowed to perfuse the brain.

When long periods of cerebrovascular occlusion

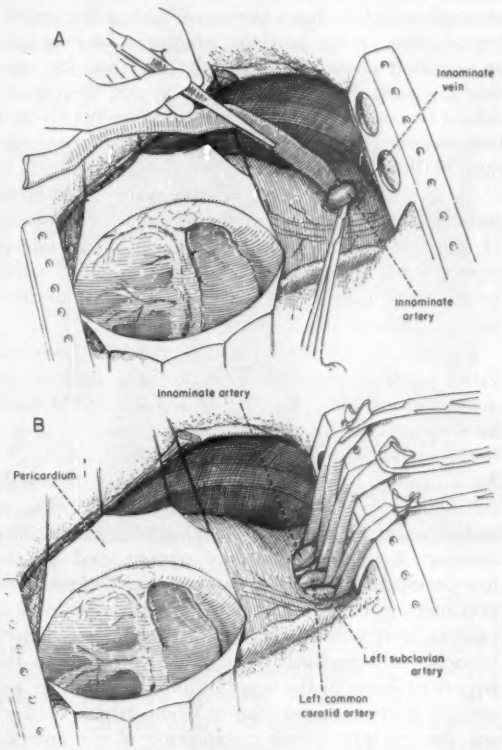

FIGURE 2. *Procedure for Obtaining Obstruction of the Circulation to the Brain.*

A= *rubber-dam drain being passed around the right innominate artery; the pericardium is open, showing exposure of the atrial appendage and pulmonary artery.*

B= *rubber-dam drains around the right innominate, left common carotid and left subclavian arteries; the vessels are obstructed by traction on the drains during the dangerous portions of intracardiac manipulation.*

have been employed the patients have at times been slow to recover consciousness after anesthesia, probably because of cerebral anoxia. On other occasions obstruction of the cerebral circulation has resulted in bradycardia or even cardiac arrest after periods of obstruction of only fifteen seconds' duration. In such cases a compromise will obviously have to be made between protection of the brain and the maintenance of the cardiac mechanism.

In addition to cerebrovascular occlusion it is our practice routinely to allow a vigorous flushing of the atrium immediately before inserting the finger in all

cases. In this way we have recovered large clots that might otherwise have embolized. In addition, a wide open-ended aspirator is thrust into the lumen of the atrium before the finger is inserted; loose fragments of clot are frequently recovered in this manner as well. On some occasions, organized clot extends from the appendage down into the chamber of the atrium, making it necessary to tunnel through or around this thrombus to reach the free lumen. No attempt should be made to remove such a clot except for the loose, friable portions, which can be managed as described above. Immediately after one has successfully tunnelled through such a clot, the finger should be removed from the atrium momentarily and free bleeding allowed. By this maneuver loose clots may be flushed out.

An alternate method of management of the large intra-atrial clot is to separate the organized portion of the clot gently from the atrial wall on its lateral aspect, opening a tunnel down to the mitral valve between clot and atrial wall with the least possible manipulation of the thrombotic mass.

Embolization of friable calcium particles from the valve edges or fused commissures is a problem of major magnitude. Bolton, Maniglia and Massey[4] have documented a case of calcium embolus to the brain. We have had similar unfortunate experiences. An additional hazard during manipulation of heavily calcified valves, not previously reported, is that of embolization of calcium particles to the coronary arteries. Recently a Group 4 patient died on the first postoperative day from an acute arrhythmia. At post-mortem examination loose embolic particles of calcium were found in several of the major coronary branches and probably were directly related to the hyperirritability of the myocardium. In another patient, a thirty-year-old man in whom friable calcium was broken into during mobilization of the anterior commissure, evidence of myocardial ischemia (elevated ST segments and widened QRS complexes) immediately followed the manipulation of the valve. He was subsequently found to have a left-sided hemiplegia, and serial electrocardiograms revealed the typical changes of a posterior myocardial infarction. It seems reasonable to assume that the infarction was due to the same mechanism that produced the hemiplegia.

These experiences, as well as others, have impressed us with the great importance of avoiding manipulations in areas of friable calcification. A compromise must be made between adequate valvuloplasty and the great risk of calcium embolus. When possible, the finger pressure is directed toward the noncalcified areas of the valve, and no area of friable calcification is remanipulated once it is identified. Often, the No. 9 valvulotome can be directed between the heavy calcific masses to effect separation without embolization.

Importance of True Valvuloplasty

No single feature of the operative procedure except patient survival is more important than maximal opening of the valve orifice while leaflet function is preserved. An operation that consists merely of a dramatic, rapid cardiotomy climaxed by a brief thrust of the index finger through the stenotic orifice can no longer be considered adequate. The initial results of such dilatation may be encouraging, but symptoms frequently recur after a few months. Some years ago, in certain patients, we succeeded only in dilating the stenotic orifice. This occurred when elastic, noncalcific stenotic funnels made up of fused leaflets, chordae and papillary muscles resisted the available maneuvers of finger fracture or incision. Now, however, fracture or incision can routinely be extended to the annulus.

A frank discussion of these initial failures and their subsequent treatment will illustrate the evolution of our current operative technic. It has been necessary to reoperate in 12 such cases. Despite the poor prognosis offered by the surgeon at the time of the initial operation 7 of these patients showed clinical improvement for three to six months. Some even enjoyed temporary rehabilitation to full-time work. However, as feared at the time of their first operation, symptoms returned as the benefit of the dilatation disappeared and the narrowing of the valve once more became critical.

With the proper use of the No. 9 valvulotome and the approach through the base of the appendage or directly through the atrial wall itself an adequate opening of the valve has eventually been achieved in all these reoperated cases. In all 10 of our own patients, and in 2 previously operated on elsewhere, we have been able to enlarge the mitral orifice to an area of 3.0 to 4.0 square cm. In 9 of the 12 patients rehabilitation has been complete. The only death from reoperation occurred on the tenth postoperative day in a woman who had the most advanced pulmonary vascular disease we have encountered in over 1000 patients (1970 dynes seconds centimeters^{-5}) and in whom regurgitation was produced at the time of reoperation.

It is of considerable interest that when these patients failed to do well, active rheumatic carditis was uniformly suspected. Rheumatic carditis may be a complicating factor, but when the original operation is known to have been less than satisfactory, the surgeon must consider a renewed attempt to perform an adequate valvuloplasty.*

*The practice of making an accurate drawing and description of the valve immediately after operation has been invaluable in the evaluation of each patient's progress after operation. This has permitted a proper appraisal of technical and myocardial factors in patients who have not maintained improvement after surgery. Estimates of orifice size before and after manipulation can be made accurate to within 0.2 square cm. by periodic calibration of the index finger in artificial orifices of known area. Comments are also made on the operative diagram about leaflet flexibility, calcification, secondary stenosis, regurgitation and so forth.

A remarkable case that documents the evolution of current technics for valvuloplasty warrants comment. A thirty-two-year-old woman had a rubbery, heavily scarred valve that was dilated from 0.7 square cm. to an estimated 1.5 to 2.0 square cm. in 1951. Although she was moderately improved for two or three months it was apparent from the return of congestive heart failure that the dilated valve had contracted. Five months after the first procedure the left atrium was *re-explored through the superior pulmonary vein*. Because of the distance from the valve and difficulty with hemorrhage it was not possible to use the No. 9 valvulotome, and again blunt separation of the commissures was only partially satisfactory. Once more she failed to show satisfactory improvement. Indeed, because of joint pains and fatigue, she was treated for eight months at bed rest for rheumatic activity. Finally, intractable cough and orthopnea made it clear that pulmonary hypertension was still responsible for her difficulty. A third operation was undertaken two years after the first. By a direct approach through the atrial wall, the mitral orifice, which was again found to be narrowed to approximately 1.0 square cm., was enlarged to more than 3.0 square cm. by incision of the fused commissures with the No. 9 valvulotome. Since this time, this patient has been transformed from a chronic invalid into a symptom-free woman who cares for her two children and works as a secretary.

Recurrence of Stenosis

It must be emphasized that these few cases requiring reoperation are derived from a total experience that encompasses more than 1000 operations on the mitral valve. They are cited to emphasize the importance of adequate operation. As has been found in the follow-up study by Ellis and Harken[2] of the first 500 cases of valvuloplasty for mitral stenosis, the vast majority of patients are improved after operation, and this improvement is almost invariably maintained without evidence of recurrence of stenosis. It is emphasized that the cases in which reoperation has been necessary are not regarded as examples of refusion *of valve leaflets*. The initial operation was merely inadequate and had failed to correct the *primary stenosis* (leaflet fusion) or the *secondary stenosis* (chordae-tendineae or papillary-muscle fusion) or both.

Significant data on the matter of readherence of leaflets come from examination of hearts in patients who had an adequate valvuloplasty but who died of unrelated causes as long as five years after the original operation. In none has there been evidence of readherence of the leaflets (Fig. 3). In addition follow-up study of several hundred patients for periods now ranging up to seven years has demonstrated that the improvement, once established, is maintained except in the rare cases already mentioned. Furthermore, on pathological grounds, one would not expect adherence of the raw edges of the separated commissures since the valves are separated for a longer period in diastole than they are approximated in systole. Finally, the recurrence of mitral valvulitis with its probable bullous edema must be a rare occurrence in patients over thirty-five years of age.

Although in the overwhelming majority of patients an adequate initial opening of the valve will result in sustained rehabilitation there are a few special cases in which true recurrence of stenosis may occur. In 1 patient in our entire series advanced calcification of the leaflets reduced their mobility so markedly that clot appeared to have caused an obliteration of one of the commissures. Keyes and Lam[5] have reported a similar case. At the initial operation this thirty-seven-year-old woman was found to have an unusually heavily calcified valve. By finger dissection a fracture running out to the annulus both anterolaterally and posteromedially was effected without great difficulty. Despite this, however, the very poor mobility of these clumsy leaflets prevented the effective size of the orifice from increasing to more than a bare 3.0 square cm. After operation, nevertheless, the patient improved, progressing from a markedly restricted life to full activity for twelve months. During this time she stated that she could "do everything" and could "breathe again." She even stoked the furnace when her husband was away. However, the symptoms of pulmonary hypertension returned gradually after a year and she died in congestive heart failure twenty months after operation. Because of accurate records of the pathologic process, we did not believe that reoperation had anything to offer this unfortunate woman. Post-mortem examination revealed com-

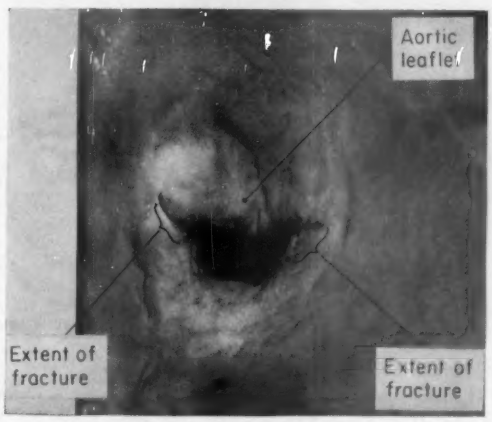

Figure 3. *Mitral Valve (Left Atrial View), Showing Persistence of Commissural Separation All the Way to the Annulus Five Years after Valvuloplasty.*

plete separation of the leaflets to the mitral annulus anteriorly. At the posterior commissure, however, in an area of heavy irregular calcification, it appeared that thrombus had formed between the valve edges, producing a recurrence of a part of the original stenosis. This must be an extremely unusual situation and one that can arise only when the calcification is so massive that it precludes adequate mobilization of the valve leaflets. We have followed many other patients with almost identical lesions and found no evidence of recurrent stenosis.

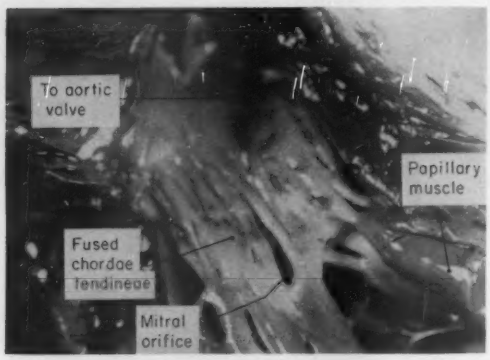

FIGURE 4. *Secondary Stenosis of the Mitral Valve. The major leaflet is seen from the ventricular surface. Fused chordae tendineae continue the stenosis down to the fused papillary muscles.*

The only other cases of recurrence of stenosis in our experience have appeared to be the result of a *traumatic endocarditis* in 2 patients in whom the efforts at blunt dissection of the commissures were of necessity moderately traumatic. The first patient in whom this process was recognized died two months after operation from the residua of a cerebral embolus. At post-mortem examination there was a rosette of fungating fibrinous and fibrous vegetation encircling the mitral orifice and producing a recurrence of stenosis. The second patient returned two years after the initial operation with evidence of recurrent stenosis, presenting a similar fungating rosette about the orifice. In this case it had become calcific. The original pathologic process was described at the first operation as a supple, elastic funnel of stenosis without any calcification. It is believed that the process described in the first patient had also occurred in the second and had become calcified in the two-year interval between operations. These rare experiences emphasize the danger of excessive palpation, dilatation with a padded finger or rough, bare-finger manipulation. They point up the importance of delicate and clean fracture or incision.

CURRENT TECHNIC

With the background of the experiences described above, emphasis has now passed beyond the early phase of commissurotomy or the separation of the fused commissures in the *"primary stenosis."* It is now recognized that in addition to this primary zone of narrowing, a *"secondary stenosis"* may exist as the result of fusion of the chordae tendineae and papillary muscles below the leaflet level. This has been found in nearly half the patients (Fig. 4).

It was important in the early phases of this surgery to appreciate the different functions of the two mitral leaflets and to preserve or restore these functions. Originally, we were too pessimistic about dealing with some of the more advanced phases of secondary stenosis (pathological Type 2 of earlier publications[6,7]). Others were even more unrealistic in trying to deal with such lesions with hook or guillotine valvulotomes. Now a technic is available that assures complete separation of the commissures out to the annulus in virtually all cases, together with mobilization of the valve leaflets by freeing of restricting moorings — fused chordae tendineae and papillary muscles (see Fig. 8 and 9).

Surprisingly enough, calcified valves seldom resist simple finger fracture. Scarred, elastic orifices without calcification are more refractory to blunt dissection but can be opened with the No. 9 valvulotome (see Fig. 6*D*).

As noted in earlier reports the stenotic orifice is rarely located at the midpoint of the leaflet margins. It is commonly posterior and occasionally anterior to this point. In any event, because the fusion of the anterior commissure is more easily separated, the posterior one should always be approached first, if it represents a significant stenotic barrier. To determine whether the fused posterior zone constitutes a significant stenotic barrier requires judgment and experience. If it is extensively fused and juts out into the atrioventricular stream it is probably significant. If it lies flush on the posterior ventricular wall it may represent no hemodynamic impedance. Finally, when it stretches like a bowstring across the posteromedial aspect of the annulus, division may be associated with a devastating degree of regurgitation. In short, the opening of the posterior fusion bridge may be *mandatory* in some cases and *elective* or occasionally *dangerous* in others.

With the fusion of the anterior commissure intact the surgeon has the advantage of working on the posterior zone under tension, whereas if the anterior fusion bridge is broken first, the leaflets become mobilized and the elastic properties of the posterior fusion bridge are accentuated. At times this area tenaciously resists standard fracture maneuvers. In such cases the surgeon may find it expedient to go around to the other side of the table (that is, facing

the anterior surface of the patient's chest) and to manipulate the posterior commissure with the right index finger. From this position it is possible to apply pressure on the edge of the aortic leaflet and, with a rolling motion, to follow the line of the former valve orifice. This often extends a surprising distance toward the midline along the posterior wall of the left ventricle.

After the satisfactory opening of the posterior commissure the anterior zone is approached. If an adequate fracture running all the way to the annulus can be obtained with the finger alone there is obviously no advantage in using a valvulotome. There is no safer and no more completely controlled method of separating the commissures than with the most

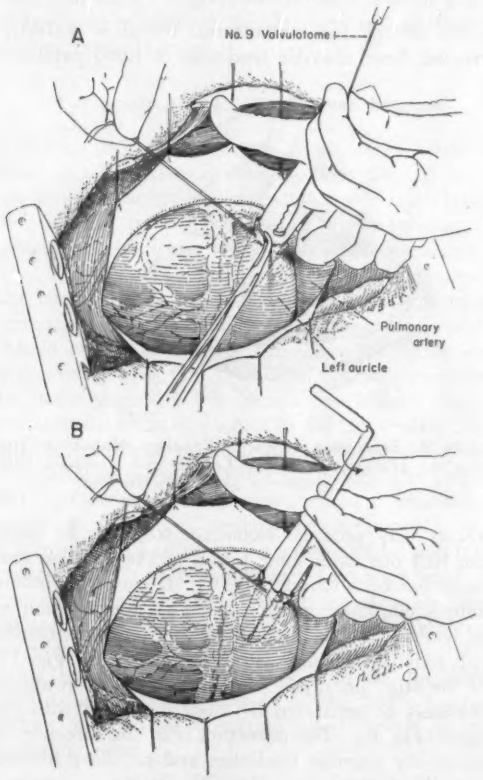

FIGURE 5. *Use of "Breadknife" Valvulotome.*
A= *No. 9 valvulotome inserted into the opened atrial appendage while an assistant retracts the edge.*
B= *valvulotome rotated 90° after the blade is safely within the free lumen of the atrium so that the shaft lies flat on the finger.*

sensitive of instruments, the finger; there is no substitute for its tactile sense. However, when a thickly scarred or elastic orifice is encountered, it is often preferable to start the commissural opening by incision and thereby avoid excessive endocardial roughening, as mentioned above. We must again warn against the use of the guillotine valvulotome. Such instruments were designed by us years ago but have been found indelicate and clumsy. Making an incision along the line of leaflet fusion is too much a matter of chance with such an instrument. Furthermore, damage to leaflets and underlying chordae tendineae, with resultant significant regurgitation, has

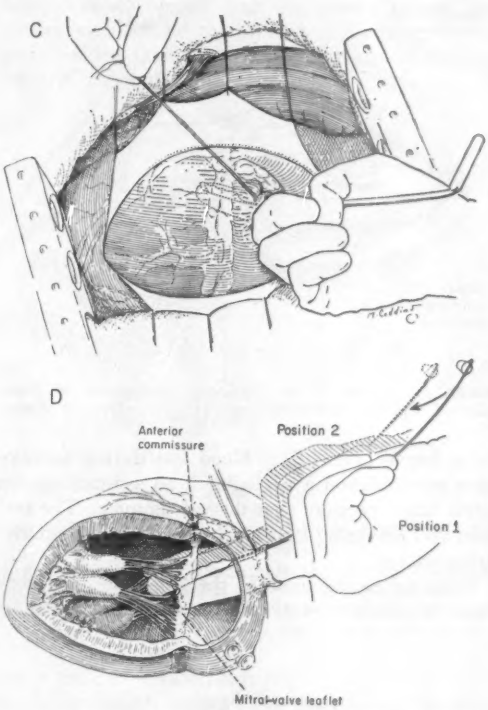

FIGURE 6. *Further Demonstration of the Valvulotome in the Heart.*
C=*valvulotome grasped with the thumb; the finger is advanced to the anterior commissure; and tactile control is maintained since the sides of the finger are in contact with the leaflets.*
D= *incision effected by advancing the finger and valvulotome forward and into the ventricle as a unit.*

occurred so often that many careful surgeons join our condemnation of this gross technic.

We have devised many valvulotomes, but by far the most satisfactory is that shown in Figures 5 and 6. It has been used to the virtual exclusion of all others for the past three years. It consists of a thin band of stainless steel, 5 mm. in width, with a short, right-angle handle. The blade consists of a "breadknife edge," which is turned 90° from the plane of the shaft. The wavy blade ensures an effective incision by presenting the cutting edge at an oblique angle to the surface to be cut. A blunt tip protects the atrium and leaflets against damage during insertion.

The valvulotome can be slipped into the atrium without the necessity of removing the operator's fin-

ger (Fig. 5*A*). No finger cot is necessary, and since the diameter of the finger is not significantly increased, no enlargement of the cardiotomy is required. The blade is inserted flat on the finger until it is within the lumen of the atrium and then rotated 90° so that the shaft comes to lie flat against the index finger (Fig. 5*B*). Blood loss during valvulotome manipulation is negligible if an assistant applies gentle finger pressure over the valvulotome. The surgeon also prevents blood loss by tightening the purse-string sutures.

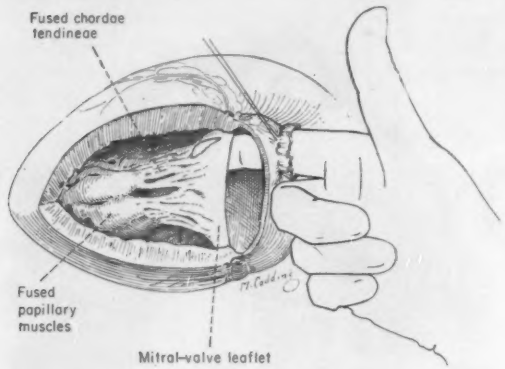

FIGURE 7. *Cut-out View, Showing Inadequacy of Commissural Opening Alone When Secondary Stenosis Exists.*

With the valvulotome in the heart the operator's finger is advanced until the fused commissure is located (Fig. 6*C*). The instrument is used with its end flush with the tip of the finger. In this way it becomes a sharpened margin for the finger. Tactile control is maintained since the finger is constantly in contact with the valve edges. The instrument is not used as a saw, sliding up and down on the finger as some have thought, but is *moved with the finger as a unit* (Fig. 6*D*). With even application of pressure in the direction of commissural fusion combined with a thrust of the finger forward and downward into the ventricle, an incision can invariably be initiated. Finger dissection may then carry the opening to the annulus. The proper use of this instrument has solved the difficult problem of the flexible funnel of stenosis formerly either inadequately handled by dilatation, traumatically ruptured by finger fracture or incised at the expense of regurgitation with the guillotine.

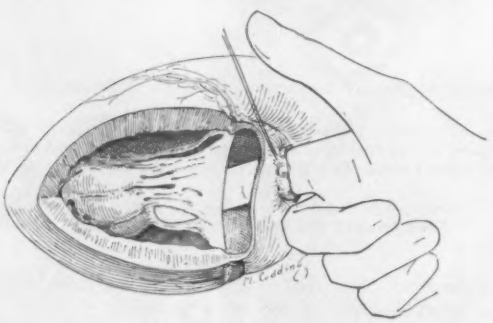

FIGURE 8. *Separation of Fused Chordae Tendineae to Improve the Mobility of the Leaflets and to Begin Correction of Secondary Stenosis.*

After adequate opening of the commissures as far as the annulus of the mitral ring most mitral-valve leaflets will show excellent mobility and valve function unless heavy calcification is present. By use of the maneuvers prescribed, regurgitation is only rarely produced and is then only of a minor degree.

Secondary Stenosis

Even though the commissural fusion is perfectly corrected, fused chordae tendineae or fused papillary muscles may produce secondary stenosis. In more than half our cases some fusion of the chordae tendineae has been found (Fig. 4). If commissurotomy alone is employed in such cases the mobilization of the leaflets will be inadequate since this maneuver deals only superficially with the obstruction (Fig. 7). On the other hand this secondary stenosis can almost invariably be separated by blunt dissection with the finger (Fig. 8). The dissection is in the direction of axis of the chordae tendineae and papillary muscles from above downward (Fig. 9). It is generally undesirable to cut them with a valvulotome, for this almost invariably results in overwhelming regurgitation.

FIGURE 9. *Separation of Fused Papillary Muscles to Improve the Mobilization of the Leaflets and Complete Correction of the Secondary Stenosis.*

As the fracture of the anterior fusion bridge approaches the annulus, careful palpation will frequently reveal crossfusion of chordae tendineae. This mild but significant secondary stenosis must be separated. A forward motion in the direction of the cardiac apex often opens the limiting leaflet moorings (Fig. 8). When this separation is properly done it is remarkable how much greater the effective valve orifice becomes, and yet no regurgitation is allowed.

In 1947 the word "valvuloplasty" was coined to describe the surgical correction of mitral stenosis. This term was chosen advisedly to emphasize the fact that an effort was being made to restore *valve function*. It was employed to call attention to the fact that stenosis was not to be corrected at the expense of regurgitation and to emphasize the importance of the total valve complex involved in the obstruction, not just the fused commissures. Only by adequate mobilization of the leaflets and by separation of the fused commissures all the way out to the annulus of the mitral ring, correction of fusion of the chordae tendineae and meticulous liberation of secondary stenosis at the level of the papillary muscles can adequate valve function be restored. Anything less than that will lead to a compromised result. "Valvuloplasty" is intended to connote the surgeon's best possible effort to restore function.

Combined Aortic and Mitral Stenosis

Often, there is auscultatory evidence of aortic stenosis as well as mitral stenosis. The decision to operate on the aortic stenosis when the mitral obstruction is being treated becomes an important one. In general, if the aortic lesion is not severe enough to give electrocardiographic evidence of enlargement of the left ventricle *and* a delayed upstroke time in the tracing of the brachial artery, the aortic stenosis should not be operated upon. However, when such evidence suggests that the aortic stenosis may indeed be hemodynamically significant, we believe that simultaneous pressure tracings in the left ventricle and base of the aorta, taken at the operating table, help decide for or against aortic valvulotomy. As pointed out by Gorlin et al.[8] it appears that a gradient of more than 50 mm. of mercury across the aortic valve is a significant burden to the left ventricle, and myocardial work is inordinately increased with small increments above this level. When an adequate blood pressure and clinical evidence of normal circulation are present, and a gradient across the aortic valve of more than 50 mm. of mercury is found, the aortic obstruction is fracture dilated by the finger fracture technic through an operating tunnel sewed on the ascending aorta.

Simultaneous Mitral and Tricuspid Valvuloplasty

Many cardiologists have pointed out that tricuspid stenosis is practically never seen without associated mitral stenosis. Nevertheless, true tricuspid stenosis in an experience involving more than 1000 patients with deformities of the mitral valve has been impressively rare. In this experience tricuspid stenosis has been suspected more than 30 times. This diagnosis was suggested by a diastolic murmur in the tricuspid area that increased with inspiration, enlargement of the right atrium and suffusion of the face when the patient was recumbent. In some cases the diagnosis was disregarded when cardiac catheterization failed to reveal a pressure gradient across the tricuspid valve. In others, in which a gradient was found, the tricuspid valve was explored at the same time that the mitral stenosis was corrected.

Early in our experience a patient with the combined valvular lesion had the mitral stenosis corrected initially, and then nine months later, through a right-sided thoracotomy, the tricuspid stenosis was opened. Since that time, however, we have been using a technic that permits exploration of the right as well as the left atrium at the same operation when there is any question of tricuspid stenosis. This approach avoids the necessity of a trans-sternal incision, which adds considerably to the physiologic derangement by opening both pleural cavities.

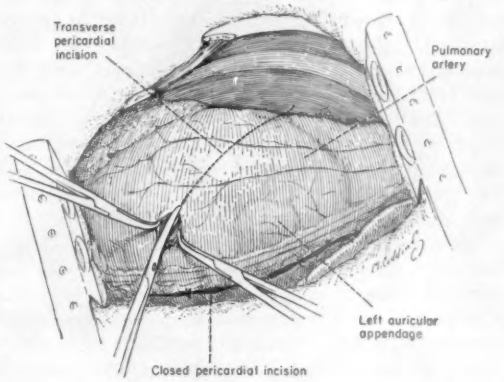

Figure 10. *Technic for Tricuspid-Valve Exploration after Mitral Valvuloplasty.*

A pericardial incision posterior to the phrenic nerve used for the mitral procedure is loosely approximated below. A second, oblique incision across the base of the pulmonary artery exposes the tip of the right atrial appendage.

By exploring the right atrium in all questionable cases we have come to appreciate the great difficulty in differentiating clinically tricuspid stenosis from insufficiency. In fact, of the 7 cases of simultaneous exploration of the tricuspid and mitral valves, true tricuspid stenosis has been found in only 3 and was even absent in 1 patient in whom a gradient of 5 mm. of mercury across the tricuspid valve was reported at cardiac catheterization. Because the additional exploration of the right atrium adds little to the risk of mitral valvuloplasty we do not hesitate to employ it whenever there is a reasonable question of tricuspid stenosis.

Technic

The left pleural space is opened by a routine lateral thoracotomy such as is used for all mitral-valve surgery (Fig. 1*B*). After the mitral stenosis has been corrected the pericardial incision posterior to the left phrenic nerve is closed, and an incision is then made

anterior to the nerve that courses obliquely across the base of the pulmonary artery (Fig. 10). By traction on marsupializing sutures placed in the edges of the incised pericardium the heart is rotated to the left, bringing the right atrial appendage into view (Fig. 11). Two opposing purse-string sutures of 0 silk are then placed around the base of the right atrial appendage, a noncrushing clamp applied, the tip excised and the right index finger introduced in a

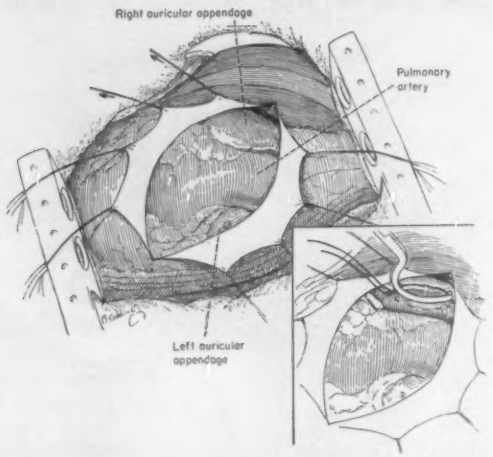

FIGURE 11. *Traction on the Marsupializing Sutures in the Pericardium to Rotate the Heart to the Left and Improve Exposure of the Right Atrial Appendage.*

Insert = two opposing purse-string sutures being placed in the right atrial appendage. The remainder of the tricuspid valvuloplasty is identical with the mitral procedure.

manner comparable to that used on the left (Fig. 11, insert). Exploration of the valve and correction of any existing stenosis is then carried out. The No. 9 valvulotome may be used exactly as described for the mitral valve. The only points of difference in this exposure over the left atrial approach are that the wall is thinner, necessitating greater care to avoid tears, and that there are more trabeculae to be divided before the finger is introduced.

Neptune and Bailey[9] have reported a case of simultaneous mitral and tricuspid commissurotomy through a right-sided thoracic approach, the posterior wall of the left atrium being entered for exploration of the mitral valve and the tricuspid stenosis being corrected through the right atrial appendage. They comment that this approach to the mitral valve is less satisfactory than that from the left, and that the use of the guillotine valvulotome is more difficult from this side. It appears quite undesirable to employ this approach for presumed mitral and tricuspid stenosis, for one would in most cases be compromising the correction of the known lesion (mitral stenosis) for the purpose of easy exploration of a lesion that might not exist. With the use of the left-sided approach described above, no compromise with optimal correction of the mitral stenosis need be made, and, in addition, one can perform a safe and satisfactory tricuspid valvuloplasty. Preoperative and postoperative cardiac catheterization have demonstrated the efficiency of this operation.

SUMMARY AND CONCLUSIONS

As the surgical correction of mitral stenosis becomes widely practiced it seems timely to re-examine the purpose of such operations and to review certain technical steps that may improve the *quality* of this surgery. The importance and technic of true valvuloplasty in restoring valve function as opposed to mere commissural incision are emphasized. The problems of embolus with reference to the clotted atrium and the heavily calcified valve are discussed. The difference between commissural fusion in *primary stenosis* and the rubbery funnel with fusion of chordae tendineae and papillary muscles in *secondary stenosis* is outlined. The importance of, and the methods currently in use for, the correction of this secondary narrowing are described.

Methods of determining hemodynamically significant aortic stenosis and therefore the place for combined aortic and mitral-valve surgery are reviewed.

Finally, a new approach for the simultaneous exploration of the mitral and tricuspid valves without opening of both pleural spaces is presented.

REFERENCES

1. Black, H., and Harken, D. E. Safe conduct of patient through cardiac surgery: with special reference to diseases of mitral and aortic valves. *New Eng. J. Med.* **251**:45-51 and 85-91, 1954.
2. Ellis, L. B., and Harken, D. E. Clinical results in first five hundred patients with mitral stenosis undergoing valvuloplasty. *Circulation* **11**:637-646, 1955.
3. Glenn, W. W. L., Shannon, J. M., and Turk, L. M. Mitral valvulotomy through rubber diverticulum. *Ann. Surg.* **140**:741-747, 1954.
4. Bolton, H. E., Maniglia, R., and Massey, F. C. Calcific emboli complicating mitral valve commissurotomy: report of case. *J. Thoracic Surg.* **24**:502-509, 1952.
5. Keyes, J. W., and Lam, C. R. Recurrence of mitral stenosis following commissurotomy. *J.A.M.A.* **155**:247, 1954.
6. Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F., III. Surgery of mitral stenosis. III. Finger-fracture valvuloplasty. *Ann. Surg.* **134**:722-742, 1951.
7. Harken, D. E., Ellis, L. B., Dexter. L., Farrand, R. E., and Dickson, J. F., III. Responsibility of physician in selection of patients with mitral stenosis for surgical treatment. *Circulation* **5**: 349-362, 1952.
8. Gorlin, R., Matthews, M. B., McMillan, I. K., Daley, R., and Medd, W. E. Physiological and clinical observations in aortic valvular disease. *Bull. New Eng. M. Center* **16**:13-23, 1954.
9. Neptune, W. B., and Bailey, C. P. Mitral commissurotomy through right thoracic approach: technique and indications. *J. Thoracic Surg.* **28**:15-22, 1954.

ADDITIONAL REFERENCES

Harken, D. E., Ellis, L. B., and Norman, L. R. Surgical treatment of mitral stenosis. II. Progress in developing controlled valvuloplastic technique. *J. Thoracic Surg.* **19**:1-15, 1950.
Love, D. E., and Levine, S. A. Mitral stenosis with long-lasting congestive heart failure or auricular fibrillation. *New Eng. J. Med.* **247**:917-920, 1952.

FAILURE OF CHEMOTHERAPY TO PREVENT THE BACTERIAL COMPLICATIONS OF MEASLES*

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SECONDARY bacterial infection is the commonest complication of measles. The development of potent antibacterial agents has made available a group of drugs that can prevent as well as cure bacterial infection. Since the introduction of the sulfonamides various agents have been used for the prophylaxis of microbial invasion in rubeola. Holbrook[1] and Coburn[2] reported that sulfadiazine eliminated bacterial complications in this disease. Failure to prevent the development of bronchopneumonia by sulfathiazole was recorded, however, by Gible and Litvak.[3] Favorable results were observed by Karelitz and his co-workers[4,5] after the prophylactic application of procaine penicillin, chlortetracycline (Aureomycin), and benzethacil (Bicillin) in measles; almost complete elimination of secondary infection was noted.

Since all the reports of the chemoprophylaxis of measles have concerned hospitalized patients and because such treatment is actually most often applied at home by the practicing physician, it was considered worth while to investigate the influence of chemotherapy given before hospitalization in the pre-eruptive and eruptive stages of rubeola on the number and type of complications present at the time of admission of patients to the hospital. For comparison, the course of untreated measles in the hospital was also studied, both in cases in which bacterial infection did not occur and in those in which it did develop and was treated with an antimicrobial agent. It is the purpose of this paper to point out that chemoprophylaxis with various antibiotic agents does not prevent the appearance of bronchopneumonia or otitis media during rubeola, that the bacteria involved in the secondary infections that occur despite chemoprophylaxis are different from those found in the same type of complication in untreated cases, and that superinfection follows the use of antimicrobial therapy for the treatment of secondary bacterial infections that develop during the course of measles.

METHODS

Four hundred and twenty-eight patients who were admitted to the Haynes Memorial Hospital with measles were the subjects of this study. All of them were personally observed during their entire hospital stay. In addition to complete physical examinations and routine studies of the blood and urine, culture of the nose and throat on blood agar and in blood broth was carried out in every case; in patients with drainage from the ears, the exudate was cultured. In all cases in which bacterial infections were present bacteriologic study of the nose and throat was performed at least every other day. Roentgenograms of the chest were taken in every case in which the possibility of bronchopneumonia was suspected. No patient was considered to have a secondary bacterial infection, despite the isolation of pathogenic bacteria from the upper respiratory tract, unless there was fever of appreciable degree and the white-cell count was elevated to 10,000 or more or, if the count was normal, there was a definite preponderance of neutrophils.

Information concerning the type of agent, dose and length of treatment used in patients given chemotherapy at home was obtained in detail from the referring physician. Only the cases in which an antibiotic was first administered in the absence of any evidence of secondary infection while the patient was at home were included in this study; all in which there was even a slight suspicion that a bacterial complication was present at the time chemotherapy was initiated before hospitalization were excluded.

RESULTS

Of the 428 patients studied 350 had no evidence of bacterial infection, and 78 had definite superimposed bacterial disease at the time of entry to the hospital. Thus, 24.6 per cent were admitted because of a complication due to microbial invasion. Although this rate of bacterial infection is higher than that usually observed in patients with measles treated at home, it probably was not completely attributable to the fact that complicated cases of rubeola were much more frequently hospitalized than uncomplicated ones because the ratio of uncomplicated to complicated measles in this study was 3:1.

Influence of Antibiotics before Admission

One hundred and thirty patients had received a variety of antibacterial agents for varying periods during the pre-eruptive or eruptive stages of measles, or both, before admission to the hospital. Of these, 36 (30.4 per cent) were found to have secondary bacterial infections when they were hospitalized. Of 298 cases in which no antimicrobial agent had been given before entry 42 (14.9 per cent) had clear-cut evidence of bacterial disease when they were admitted to the hospital. These data suggest that the use of antibiotic agents in these patients at a time in the course of rubeola when there was no evidence of secondary infection not only did not prevent the ap-

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pearance of this complication but also may actually have increased the risk of its development because bacterial disease was twice as frequent in the treated as in the untreated cases. Of the total of 78 patients who entered the hospital with complicated measles, 36 (46 per cent) had received some kind of antimicrobial drug before the bacterial infection developed.

Data concerning the type and duration of therapy as well as the day of treatment on which bacterial infection appeared are presented in Tables 1 and 2. Procaine penicillin was the agent employed most commonly both in cases in which complications developed and in those in which they were absent. The broad-spectrum antibiotics were also given, alone or in combination with other drugs. Secondary infections occurred most often between the third and fifth days of antibiotic administration; this period has been reported by Weinstein et al.[6] to be the one of greatest frequency of superinfection after chemotherapy. None of the patients had been treated for less than two days before hospitalization. Some had received antimicrobial agents for as long as a week because therapy was undertaken for the fever at the beginning of the prodromal phase of measles and continued into the eruptive phase.

The secondary infections that occurred in antibiotic-treated and untreated patients were different both in type and in frequency (Table 3). Pneumonia developed in 77.8 per cent of those given chemoprophylaxis and in 57 per cent of those who did not receive a drug. Otitis media, on the other hand, was more common when antimicrobial agents were not used. This observation confirms the previously recorded[6] high degree of susceptibility of the lungs to superinfection in the course of chemotherapy. Laryngotracheobronchitis was observed only in untreated cases.

Haemophilus influenzae was the commonest cause of secondary bacterial infection in treated patients and was responsible for the superimposed disease over two and a half times more often than in patients who had not received prophylaxis. The organisms most frequently responsible for complications when antibiotics were not given were the pneumococcus, beta-hemolytic streptococcus, *Staphylococcus aureus* and *H. influenzae*, the occurrence of each being approximately the same (21 to 23 per cent). Of importance from the standpoint of possible difficulty in management were the patients with measles who had received antimicrobial agents and manifested infections due to *Klebsiella pneumoniae, Escherichia coli,* anaerobic streptococci and monilia; 1 treated patient was infected with proteus (Table 4). These data confirm previous observations concerning the fre-

TABLE 1. *Patients with Measles Entering the Hospital with Bacterial Complications after Therapy with Antibiotic Agents.*

Type of Therapy	No. of Patients
Penicillin	18
Chlortetracycline	4
Tetracycline	4
Chloramphenicol	2
Oxytetracycline	1
Sulfadiazine	2
Penicillin & streptomycin	1
Penicillin & erythromycin	1
Penicillin & tetracycline	1
Penicillin & chloramphenicol	1
Penicillin & chlortetracycline	1

Interval before Complication Occurred	
days	no. of patients
2	3
3	7
4	12
5	7
6	3
7	3
8	1

TABLE 2. *Patients with Measles Given Antibiotics during Prodrome or Rash and Admitted to the Hospital without Complications.*

Type of Therapy	No. of Patients
drug	
Penicillin	57
Chlortetracycline	10
Sulfadiazine	5
Oxytetracycline	4
Chloramphenicol	3
Penicillin & chlortetracycline	6
Penicillin & chloramphenicol	2
Penicillin & sulfadiazine	2
Penicillin & streptomycin	2
Penicillin & oxytetracycline	2
Chloramphenicol & chlortetracycline	1

Duration of Therapy before Admission	
days	no. of patients
2	15
3	29
4	17
5	11
6	10
7	4
>7	8

quency with which superinfections complicating chemotherapy are provoked by organisms that are relatively more resistant to treatment than those responsible for infections in persons who are not exposed to antibiotic drugs.

Secondary Infections in Patients Not Treated after Entry

Three hundred and fifty patients entered the hospital with no evidence of secondary bacterial infection; of these, 256 had not and 94 had received chemotherapy before admission. None of these patients were treated with an antibiotic after hospitalization until there was clear-cut evidence of superimposed bacterial disease. Sixteen patients (4.6 per cent) manifested secondary bacterial invasion during their residence in the hospital. Table 5 shows the types of disease that appeared and the organisms that were isolated. Pneumonia and suppurative

TABLE 3. *Type of Secondary Bacterial Infections in Patients Entering the Hospital with Bacterial Complications.*

SECONDARY INFECTION	PATIENTS TREATED BEFORE ENTRY	PATIENTS NOT TREATED BEFORE ENTRY
Pneumonia	28(77.8%)	24(57.1%)
Otitis media	5(13.8%)	10(23.8%)
Pharyngitis	2(5.6%)	3(7.2%)
Lymphadenitis	1(2.8%)	0 —
Laryngotracheobronchitis	0 —	5(11.9%)
Totals	36	42

otitis media were the commonest lesions, and the bacteria involved most frequently were the pneumococcus, *H. influenzae,* the beta-hemolytic streptococcus and *Staph. aureus.*

It is interesting to compare the frequency of bacterial infection in untreated rubeola at home and in the hospital. In the patients included in this paper, the risk of development of this type of complication at home appeared to be about three times greater than it was in the hospital. Although this suggests that chemoprophylaxis may be more necessary for the patient with measles who is not hospitalized, bacterial infections actually occurred more than twice as frequently in patients at home who received chemotherapy than in those who remained untreated. The reduced frequency of secondary infection in the hospital may merely be the result of strict isolation and separation of these patients, with less exposure to pathogenic organisms that may be carried by members of a family, especially in the winter and early spring.

Superinfections

The 78 patients who entered the hospital with bacterial complications and the 16 who had them after hospitalization were all treated with antibiotics. Of this group of 94, 11 (11.6 per cent) had clinical and bacteriologic evidence of a new infection that occurred during the period of therapy. These data emphasize the risk of chemotherapy in measles; the rate of superinfections after the administration of antibiotics in a large variety of other infections averages about 2 per cent.[6] The primary infections and the causative organisms for which treatment was

TABLE 4. *Bacteria Responsible for Secondary Infections in Patients Entering the Hospital with Bacterial Complications.*

ORGANISM	PATIENTS TREATED BEFORE ENTRY	PATIENTS NOT TREATED BEFORE ENTRY
H. influenzae	21(58.2%)	9(21.4%)
Staph. aureus	4(11.1%)	10(23.8%)
Beta-hemolytic streptococcus	2(5.6%)	10(23.8%)
Anaerobic streptococcus	1(2.8%)	0 —
K. pneumoniae	1(2.8%)	0 —
Pneumococcus	1(2.8%)	9(21.4%)
Esch. coli	1(2.8%)	0 —
Proteus	0 —	1(2.4%)
Monilia	1(2.8%)	0 —
Not identified	4(11.1%)	3(7.2%)

instituted, as well as the type, etiology and time of development of the superinfection, are presented in Table 6. Pneumonia was the commonest complication of measles in which treatment was followed by the appearance of superinfection. The organisms responsible for the pneumonitis for which therapy was instituted were *H. influenzae,* the pneumococcus, the

TABLE 5. *Type of Secondary Infection and Organisms Involved in Untreated Hospitalized Cases of Measles.*

ORGANISM INVOLVED	PNEUMONIA	OTITIS MEDIA	PHARYNGITIS
	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Pneumococcus	4	1	—
Beta-hemolytic streptococcus	1	0	1
Staph. aureus	1	1	—
H. influenzae	1	4	—
Unidentified	1	1	—
Totals	8	7	1

beta-hemolytic streptococcus and *Staph. aureus.* The superinfections were due to monilia, *H. influenzae, Esch. coli, Staph. aureus* and proteus. All these organisms were obviously insensitive to the antibiotic agent used initially. Of especial interest are the infections due to *Staph. aureus* that developed during the period of penicillin administration. Such organisms, as well as monilia and proteus, may be difficult to eradicate. It is striking that the rate of superinfections (11 per cent) was more than twice as high as that of bacterial infections (4.6 per cent) in untreated hospitalized patients with measles. This is almost identical to the ratio of infections that occurred in treated and untreated patients at home.

Discussion

The data presented indicate that in the group of patients studied, the use of antimicrobial drugs during the pre-eruptive or eruptive stage of measles did not prevent the development of secondary bacterial infection. In fact bacterial invasion was more than twice as frequent in patients treated at home as in those not treated before hospitalization and over seven times more frequent than in patients who received no chemoprophylaxis after admission to the hospital. These differences cannot be explained on the basis of more frequent hospitalization for complicated rubeola because, in this series, the ratio of patients with secondary infections to those without such infections on admission was 1:3. The high rate of complications accompanying the use of antibiotics prophylactically may be related to the nature of the primary disease and the age of the patients. Pulmonary conditions such as the bronchitis of measles and young age are factors that predispose to the development of superinfection.[6,7] Quite striking was the relative infrequency of bacterial infections during the period of hospitalization in patients who had no complications at the time of admission. The possible significance of isolation from carriers of pathogenic organisms as an explanation of this phenomenon has already been commented upon.

The observations recorded in this paper indicate that in a great many patients with measles antimicrobial therapy not only is ineffective in preventing bacterial complications but also may increase the risk of their development. Since, in addition, infections occurring during chemoprophylaxis may be due to organisms that are relatively drug resistant, and since the administration of any of the antibiotic agents is accompanied by a varying risk of some type of reaction, it appears not only unnecessary but also possibly even unwise to administer chemotherapeutic agents to patients with rubeola until there is definite evidence of a treatable secondary bacterial complication. Antimicrobial substances are often given not for the purpose of prophylaxis but rather for treatment in the prodromal phase of measles under the mistaken impression that the symptoms are due to bacterial infection. It may be very difficult to distinguish between the two without laboratory studies, which may be difficult to carry out; a history of exposure to measles is helpful but not entirely conclusive. The decision must rest entirely on the judgment of the physician, who is aware of the risks involved in the use of antibacterial agents. Unfortunately, however, parents and patients often insist on the use of antibiotics in the presence of fever or what appears to be respiratory-tract infection, and it may be difficult for the physician to refuse this demand.

Table 6. *Characteristics of the Superinfections in Secondarily Infected Measles Treated with Antibiotics.*

Complication	Organism	Treatment	Superinfection	Organism	Day of Treatment On Which Superinfection Appeared
Otitis media	Staphylococcus	Penicillin & streptomycin	Stomatopharyngitis	Monilia	5
Otitis media	?	Penicillin	Pneumonia	*H. influenzae*	4
Pneumonia	Pneumococcus	Penicillin & streptomycin	Pneumonia	*Esch. coli*	5
Pneumonia	*H. influenzae*	Streptomycin	Stomatopharyngitis	Monilia	3
Pharyngitis	Beta-hemolytic streptococcus	Penicillin	Pharyngitis	*H. influenzae*	6
Pneumonia	Pneumococcus	Penicillin	Otitis media	*H. influenzae*	7
Pneumonia	Pneumococcus	Penicillin	Pneumonia	*H. influenzae*	6
Pneumonia	Beta-hemolytic streptococcus	Penicillin	Pneumonia	*Staph. aureus*	5
Otitis media	Beta-hemolytic streptococcus	Penicillin	Otitis media	*Staph. aureus*	4
Pneumonia	Pneumococcus	Penicillin	Pneumonia	*H. influenzae*	5
Otitis media	Staphylococcus	Penicillin	Otitis media	Proteus	5

Summary and Conclusions

Four hundred and twenty-eight patients admitted to the hospital with measles were studied for the presence of bacterial infection in relation to the administration of antibiotics.

Of 130 patients hospitalized after having received chemotherapy at home before the development of bacterial infection, 30.4 per cent had secondary bacterial disease at the time of admission. This complication was present in only 15 per cent of 298 cases in which no antimicrobial agent had been used before hospitalization.

In 350 patients (256 received no drug and 94 were treated *before* hospitalization) not treated *after* admission to the hospital the rate of secondary bacterial infections was 4.6 per cent.

Haemophilus influenzae was the organism most frequently responsible for secondary infection in pa-

tients who had received antimicrobial therapy; the pneumococcus, beta-hemolytic streptococcus, *Staphylococcus aureus* and *H. influenzae* were the most common etiologic agents when drugs were not administered.

Of 78 patients who received chemotherapy after entry to the hospital a superinfection developed in 11 per cent during the course of treatment.

Despite the fact that the patients described in this paper are a somewhat selected group and represent only a fraction of cases of measles treated by physicians at home, the data presented strongly suggest that antimicrobial agents do not prevent the development of serious bacterial infection during the course of rubeola and that their use may actually be associated with an increased risk of development of this complication.

References

1. Holbrook, W. P. Army Air Forces rheumatic fever control program. *J.A.M.A.* **126**:84-87, 1944.
2. Coburn, A. F. Prevention of respiratory tract bacterial infections by sulfadiazine prophylaxis in United States Navy. *J.A.M.A.* **126**: 88-93, 1944.
3. Gibel, H., and Litvak, A. M. Sulfathiazole in treatment of measles and its complications. *J. Pediat.* **21**:315-320, 1942.
4. Karelitz, S., King, H., Curtis, B., and Wechsel, M. Use of aureomycin and penicillin in treatment of rubeola in pre-eruptive and early eruptive phase. *Pediatrics* **7**:193-199, 1951.
5. Karelitz, S., Chang, C. C., and Matthews, Z. E. Prophylaxis and treatment of bacterial complications of measles with benzethacil and aqueous procaine penicillin g. *J. Pediat.* **44**:357-363, 1954.
6. Weinstein, L., Goldfield, M., and Chang, T. Infections occurring during chemotherapy: study of their frequency, type and predisposing factors. *New Eng. J. Med.* **251**:247-255, 1954.
7. Weinstein, L., Seltser, R., and Marrow, C. T., III. Treatment of pertussis with aureomycin, chloramphenicol, and terramycin. *J. Pediat.* **39**:549-559, 1951.

SODIUM DIATRIZOATE FOR INTRAVENOUS PYELOGRAPHY*

A Report of 100 Cases

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As urologists and radiologists we are interested in devising safer and better methods of urologic examination. The opportunity was presented to us a short time ago to use sodium diatrizoate†† as a new radiopaque contrast medium for intravenous pyelography. The substance had previously been used by Moore and Mayer[1] with good results, and it was considered for trial in this hospital. Martineau, Forsythe and Soderberg[2] had likewise reported 100 cases, with significantly better films.

Accordingly, we collected 100 cases, which are presented in this paper. Our results are considered to show a significant improvement in film contrast with a minimum percentage of reactions.

The 100 patients ranged in age from one and a half to ninety-two years, 70 being males and 30 females. The contrast medium was given intravenously in all cases except 1, in which an intramuscular injection of 30 cc. was given to a one-and-a-half-year-old child. In the other four children 15 to 30 cc. was injected intravenously. In all other cases the full 30-cc. dose was given intravenously.

All films were examined by the team of urologists and roentgenologists in our group.

The qualitative results of the films obtained are listed in Table 1. For the purpose of this report the cases were divided into three age groups.

Table 1. *Quality of Excretory Pyelograms in 100 Cases.*

Age Group	Excellent Result	Good Result	Fair Result	Poor Result	Totals
	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases
yr.					
1½ to 16	2	2	1	—	5
16 to 50	8	22	2	—	32
50 to 92	5	39	8	11	63
Totals	15	63	11	11	100

Thus, the diagnostic procedure resulted in 78 films (78 per cent) with excellent or good results. The total number of films that could be used for diagnostic purposes was 89 (89 per cent); of 11 films that were not useful for diagnostic purposes 8 had been poorly prepared. There were 2 patients whose motion during the taking of the film disturbed the picture, and there was 1 patient with a high nonprotein nitrogen.

Of particular interest is the intramuscular injection of 30 cc. of sodium diatrizoate, complemented with hyaluronidase, in a one-and-a-half-year-old child. The substance was rapidly excreted in ten minutes, and there was good contrast and filling in

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the twenty-minute film. This intramuscular injection was well tolerated, and the quality of the film was excellent. Figure 1 demonstrates this contrast, which allowed a diagnosis of crossed renal dystopia. Figure 2 is a representative excretory urogram in an adult.

It is our impression that the increase in contrast in the films and the increase in the rate of excretion of this new radiopaque medium improved the diagnostic character of the excretory pyelograms.

FIGURE 1. *Intramuscular Pyelogram, Taken with Sodium Diatrizoate, in a Child with Crossed Renal Dystopia.*

Table 2 lists the side effects observed. A total of 20 patients had mild to transient, and 2 had moderately severe side effects. One of the latter was a woman with a previous history of asthma and hypothyroid disease. After severe nausea and vomiting developed the injection had to be temporarily stopped. However, the symptoms subsided, and she was given the full 30-cc. injection. A mild venous cramp also occurred. The other moderately severe reaction developed in a forty-eight-year-old woman, who had a venous cramp after the injection had been completed. She continued to have some pain in the shoulder until the following day.

There were no side effects in the children under sixteen years of age. The mild and transient side effects in those from sixteen to fifty years old were all single, whereas in the older age group there were 13 patients with a total of 20 reactions. All of these were mild and transient, and the full 30-cc. injection was given. In 2 patients the blood pressure fell from 130 systolic, 75 diastolic, to 110 systolic, 60 diastolic, and from 190 systolic, 120 diastolic, to 180 systolic, 100 diastolic. There was 1 increase in blood pressure that we believed to be due to the patient's apprehension.

Of this total group of 100 patients there was previous history of allergy in 5, 3 of whom had no reaction. In the others 1 case was mild, and the other was the severe reaction described above in a patient with a history of allergy and hypothyroid disease.

Discussion

The material used for injection was 30 cc. of a 50 per cent solution of the medium, which is a sodium salt of an organic compound containing about 60 per cent iodine. According to Moore and Mayer[1] most of the drug is eliminated within two hours of intravenous injection, and 90 per cent is excreted in the urine within twenty-four hours in the unchanged form. The optimal time for the rate of injection of the 30 cc., with the fewest side effects, is three minutes.

FIGURE 2. *Typical Intravenous Pyelogram, Taken with Sodium Diatrizoate, in an Adult.*

Moore and Mayer[1] reported excellent or good films in 92.9 per cent of 210 unselected patients. Ninety-seven per cent of their films were diagnostic.

A total of 86.7 per cent of their patients had no side effects whatsoever. Our results were not quite so striking. Perhaps this is because our films were read and rated independently by radiologists with the caution usually accorded a new and untried preparation. Not only the excretion and contrast of the dye but also the preparation of the patient and the technic and quality of the films taken by the several technicians were considered. Thus, films that showed excellent excretion and contrast frequently received a lower grade because of less than perfect preparation or film technic. Considering these factors, it may be fairly concluded that our experience with the medium under consideration confirms the observations of the previous investigators[1,2] that this new substance affords a useful advance in excretory urography.

TABLE 2. *Side Effects.**

REACTIONS	NO. OF PATIENTS 16-50 YR. OF AGE	NO. OF PATIENTS 50-92 YR. OF AGE	TOTALS
None	24	49	78
Mild & transient:			
Sensation of warmth	3	7	
Nausea & vomiting	3	6	
Shortness of breath		2	
Venous cramp		2	
Choking sensation		1	
Decrease in body temperature		1	
Dizziness	1		
Flushing of skin		1	
Total reactions	7	20	
No. of patients	7	13	20
Severe:			
Venous cramp	1		
Vomiting, choking sensation & fatigue		1	2
Total patients	32	63	100

*No side effects in 5 patients under 16 yr.

CONCLUSION

It is our impression that sodium diatrizoate, a new radiopaque contrast medium for excretory pyelography, gives an improved contrast in the films and with the increased rate of excretion has enhanced diagnostic procedures. In a preliminary series of 100 cases the rate of reactions (20 per cent mild to 2 per cent severe) was much lower than that with other radiopaque contrast mediums that we have used.

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REFERENCES

1. Moore, T. D., and Mayer, R. F. Hypaque: improved medium for excretory urography: preliminary report of 210 cases. *South M. J.* **48**:135-141, 1955.
2. Martineau, L., Forsythe, T., and Soderberg, C. Hypaque (WIN 8303-3): new improved urographic contrast medium. Presented at the third annual Rhode Island Hospital Research Day, Providence, Nov. 10, 1954.

SPECIAL ARTICLE

SURGICAL LESIONS OF DIABETIC FEET

COMMITTEE ON DIABETES, MASSACHUSETTS MEDICAL SOCIETY*

BOSTON

A STUDY of the frequency and the cost, both financial and in terms of future disability, resulting from surgical lesions of the feet in diabetic patients was undertaken in the hope that the information thus obtained might stimulate interest in and implement measures to prevent these lesions or reduce their cost. The Committee on Diabetes of the Massachusetts Medical Society proposed in 1953 that certain hospitals in Boston equipped with a resident staff assess the frequency of these cases by recording all diabetic patients actually in the hospital wards and seen by surgeons because of surgical lesions of the feet. Co-operating hospitals and clinics included the New England Deaconess, Massachusetts Memorial, Peter Bent Brigham, Boston City, Massachusetts General, Beth Israel, Cambridge City, Burbank (Fitchburg) and the New England Baptist hospitals. In the first six months 264 patients, and in the second six months 238 patients were studied.

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AGE AND SEX

Of the total of 502 patients studied 210 were males, and 292 were females, ranging from childhood to old age (Table 1). Although 3 patients were under twenty and 18 under forty years of age, 299 were between sixty and seventy years and 22 between eighty and ninety years of age.

Duration of Diabetes

Forty-two patients (8 per cent) were not aware of the existence of diabetes before the foot lesions appeared, or else the duration was estimated at less than six months (Table 2). In 89 cases the diabetes had existed for six months to five years, and 190 patients had had the disease for five to fourteen years. One hundred and fifty-three patients had had diabetes for fifteen to thirty years.

Pathology

The cases were classified according to primary and major etiologic factors consisting of arterial insufficiency, infection, neuropathy or a combination of two or more such causes. Absence of dorsalis-pedis pulsations was noted in the feet with the lesions in 225 cases, with absence of pulsation in the popliteal less frequent and absent femoral pulsation in relatively few gravely ill patients with gangrene. A history of intermittent claudication for months or even years, in combination with the characteristic cold foot cyanotic on dependency and becoming cadaveric in appearance when raised at an angle of 45°, with venous filling time delayed beyond twenty seconds, all contributed to the diagnosis of arterial insufficiency. Patients with neuropathy almost always had open areas of infection in the toes or over a joint, occasionally with osteomyelitis. The characteristic feature in this group was the presence of adequate pulsations or at least good collateral circulation so that impaired blood supply was not a major factor. However, the patients manifested a lack of pain sensation and had usually walked on an open lesion with local dressings for periods of weeks or months. Absence of sensation, as judged by lack of normal response to pin prick or tuning fork, often with absence of knee reflexes, contributed to the diagnosis of neuropathy. In patients classified as having primarily infection the most characteristic lesion was infection arising in a corn or callus, which had often extended into bone or joint because of long neglect. In addition to this group were patients who had sustained slight trauma from heat, accidents, pressure or chemical burns followed by infection. In these patients good circulation, as judged by the presence of pulsations or lack of evidence of poor blood supply, was present. Actually 98 cases were not classified with acceptable certainty, leaving a total of 404, of which 48 per cent were classified as due to arterial insufficiency, with gangrene in 187 cases. Of this group, 200 patients, or a quarter, had infection in addition to arterial insufficiency, and another quarter had neuropathy.

Table 1. *Ages of 502 Diabetic Patients.*

Age	No. of Patients
yr.	
Under 20	3
20-39	18
40-59	160
60-79	299
80-90	22
Total	502

Thirty-three patients, or about 6.6 per cent of the total series, died. However, these 33 deaths occurred among 332 operations, giving a surgical mortality of 10 per cent. The causes of death were coronary occlusion in 5 cases, pulmonary embolism in 6, congestive heart failure in 6 and atrial fibrillation in 1, cerebrovascular accident in 2, infection and toxemia in 3, renal failure and uremia in 3 and, finally, none specified in 7. Of 10 cases post-mortem examinations revealed coronary-artery disease and myocardial infarction in 3, pulmonary embolism in 3, bronchial pneumonia in 1, pyelonephritis and septicemia in 1 each and localized peritonitis, syphilitic aortitis and cirrhosis of the liver, with esophageal varices, in 1.

Location of Lesion

Among the 502 patients lesions limited to the toes occurred in 187 (Table 3). Lesions involving the toes as well as the forefoot, the sole or the heel occurred in 174 patients, and the legs were involved in 127. Thirteen cases were not classified according to location.

Table 2. *Duration of Diabetes.*

Duration	No. of Cases
Under 6 mo. (or found on admission)	42
6 mo. to 5 yr.	89
5 to 14 yr.	190
15 to 30 yr.	153
Over 30 yr.	8
Unknown	20
Total	502

In about a third of the series (170 patients) no amputations or surgical procedure was necessary. In 81 cases amputations above the ankle were done. The remainder consisted of amputation of the toes, with or without incisions for drainage of infection in the feet. Sympathectomies were performed in 20 patients.

Hospital Stay

The average hospital stay for the entire series was twenty-six-and-six-tenths days. The hospital stay averaged only fourteen-and-two-tenths days for patients who required no operation and thirty-three-

and-nine-tenths days for patients with operations above the ankle.

The period of treatment before hospital admission was important primarily because of its character and secondly because of its duration. The prior treatment had been given on an ambulatory basis in doctors' offices or in outpatient clinics. In 79 cases previous treatment was not described in detail. However, local treatment had consisted of hot soaks, sometimes with magnesium sulfate, the use of various kinds of ointment, liniment, salves, lanolin and also much more potentially dangerous substances such as iodine, Lysol, hot Lysol soaks, sulfur napthol and Zonite.

The average hospital stay is reduced by the fact that *a good many patients* died during the first few days after operation. If these patients with short hospital stays are omitted the average hospital stay exceeds thirty days. Actually, 90 patients were in the hospital for sixty to a hundred days. A similar picture existed in the matter of treatment before hospital admission: although the average period of such treatment was only twenty-four days, the number of patients who had had a lesion less than ten days was extremely low. The number of patients who had had a lesion for a month or two before entering the hospital was large.

Diabetic Treatment

Insulin was being used on admission to the hospital by 391 patients, of whom 85 were taking 4 to 15 units, 214 from 16 to 40 units, and 90 from 42 to 94 units a day (Table 4). Four patients were taking between 100 and 120 units. The character of diabetic control was an outstanding feature. Although nearly 80 per cent of the patients had been taking insulin its use had been intermittent and without sufficient medical supervision in many cases, and as a result effective control of the diabetes (as evidenced by freedom from glycosuria, hyperglycemia and clinical symptoms) had not been obtained.

Table 3. *Location of Lesions.*

Toes	Toes & Forefoot, Sole or Heel	Legs	Unclassified
no. of cases	no. of cases	no. of cases	no. of cases
188	174	127	13

At discharge there were only 42 patients not requiring insulin. It should be emphasized that freedom from glycosuria without the use of insulin may indicate that the diabetes is mild but may not guarantee normal resistance to infection or freedom from progressive, occlusive vascular disease.

Diet

Overeating and excessive weight are predominant features in the past history of diabetic patients with foot lesions. The weights of 290 patients had ranged from 180 to 309 pounds. Table 5 gives the maximum weights.

Financial Cost

In most Boston hospitals the daily cost for treatment of patients in the hospital is approximately $24. This includes the cost not merely of board, room and nursing but also of x-ray study, electrocardiograms, all laboratory work and blood transfusions. Since these 502 patients averaged twenty-six days in the hospital wards, the cost for this hospital admission was approximately $300,000. Actually, at one hospital, 60 consecutive patients had an average daily charge of $15.50 for board and room, making a total of $31,592 for hospital service. Extra charges in the same period amounted to $15,877. The average cost per day for these 60 diabetic patients with surgical foot lesions was $24.15. If some allowance is made for the period before hospital admission, which averaged nearly thirty days, and for the period after hospital discharge, which in a considerable number of patients suffering major surgery might be a month to an indefinite loss of economic productivity, the cost for these 500 patients can be estimated at $500,000 without any allowance whatever for professional services by physicians or surgeons.

Table 4. *Insulin Dosage.*

Amount of Insulin on Admission	No. of Patients	Amount of Insulin on Discharge	No. of Patients
units		*units*	
None	95	None	42
4-15	85	4-15	65
16-40	214	16-40	208
42-94	99	42-88	115
100-200	4	90-126	9
Unknown	14	Unknown	54
		(Dead patients)	9

Table 5. *Maximum Weights of 502 Patients.*

Weight	No. of Cases
lb.	
Less than 150	52
150-179	98
180-229	196
230-309	94
Unknown	72

Discussion

Earlier diagnosis of diabetes and earlier instruction of the elderly diabetic patient in the care of the

feet is urgently needed. Diabetes that is apparently mild may be accompanied by progressive occlusive vascular disease in the older patient, and within a period of months or years the patient with so-called mild disease may suffer slight trauma followed by infection and gangrene. The fact that 50 per cent of the patients in this series had already had such severe peripheral arteriosclerosis that the dorsalis-pedis pulsations were absent indicates not only that the present condition is serious but also that the present hospital experience will be followed by hospital stays in the next few years. The complete ignorance of many diabetic patients of both their diabetes and the nature of diabetic control and the importance not merely of the use of insulin but also of frequent medical observation and finally the early care of mild lesions of the feet is still a problem. This situation calls for a concerted effort by the medical profession together with such community agencies as the Diabetes Committee of the United Community Services of Boston, visiting nurses' associations and public-health agencies to reach the diabetic public with information that they will use. The following five simple points could be presented to all diabetic patients, especially those over forty years of age, and to their families:

1. Do not walk on a sore foot.
2. Beware of the painless diabetic foot.
3. Use no heaters, drugs or chemicals without a doctor's order.
4. Procrastination steals the diabetic leg.
5. Control the diabetes with diet and insulin.

Treatment of foot lesions on an ambulatory basis was continued too long in this group. Unwarranted faith in the use of antibiotics or antiseptics in the face of serious deficiency in the blood supply is a serious hazard. This type of management should be discontinued in the presence of active or extending infection, ulcerations on weight-bearing points, ulcerations over joints that may extend into joints; infected corns or calluses that are deep and any infection in a foot with arteriosclerotic deficiency of blood supply.

The Committee is indebted to the physicians and surgeons at each of the seven hospitals co-operating in the study, who accepted responsibility for the examinations and records of the patients, and to Dr. Herbert L. Lombard and Miss Mary E. Flaherty, of the Division of Adult Hygiene, Massachusetts Department of Public Health, who helped with the statistical analysis of the results.

MEDICAL PROGRESS

STATISTICAL METHODS IN MEDICINE (Concluded)

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ANALYSIS OF RESULTS

Measurement

Sufficient reference has already been made to the importance of ensuring that any two compared measurements are made on individuals or groups that are meaningfully comparable. It must further be ensured that the measurements themselves are derived in comparable ways — in other words, in such ways that any differences reflect real differences between the things measured and not merely differences in the technics of measurement. For many objective measurements there is no great difficulty on this score, sex, age, temperature and the presence or absence of specific disease, for instance, being usually determinable with little error. However, for many objective characteristics greater difficulty may be encountered. The importance of "blind" assessment of x-ray films and other findings whose measurement is debatable was mentioned in the first section of this report in connection with therapeutic trials, but similar considerations apply to all statistical data. A good example of the necessary technics is Yerushalmy's[85] comparative study of different film sizes and other variables in mass radiography. Many of the difficulties encountered in the measurement of sickness, recovery and health have been described by Stocks.[86] The difficulties are not always obvious. For instance, in a recent study,[87] the author compared the ages at death of distinguished and undistinguished American physicians, the criteria of distinction being the placing and length of obituary notices in the *Journal of the American Medical Association*. The author recognized these criteria as being only partially successful in measuring distinction, but an even more important question is whether the criteria are applied equally at all ages. Is it not possible that, for a given standard of achievement, a physician dying at the height of his career will draw a more "distinguished" obituary than one who has

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lived in retirement for twenty years and whose contemporaries have predeceased him?

The greatest difficulty comes when one attempts to measure characteristics that are dependent on the subjective interpretation of the patient or the observer, such as whether the patient feels better, worse or the same, whether or not he had a happy childhood or whether the observer thinks the patient is more or less icteric. Use can be made of such sentiments, but, in a comparison of two groups in these respects, it is not merely desirable but essential that the person whose subjective judgment is involved, either patient or observer, be unaware to which of the two groups the patient belongs. It may be argued that in certain problems this is impossible. If that is so, the study may as well be abandoned, and some other approach sought.

In this context the difficulties involved in the use of vital statistics for large areas may be noted. It should always be borne in mind that published national data do not indicate the frequency of events but the frequency with which such events are reported to the authorities. It is reasonable at least to ask, for instance, whether the recorded lower incidence of congenital malformations in Negroes compared with whites results from lower susceptibility or from lower reporting rates, and whether the excess of female births recorded in the Virgin Islands results from higher reporting rates for females in a matriarchal society. The sources of confusion in comparison of data from different countries are even more numerous. Dedrick[38] notes the difficulty in obtaining uniform definitions for such simple words as "marriage" and "household" during design of the proposed 1950 Census of the Americas, and numerous examples of spurious differences in disease incidence are given by Hill.[39]

Analysis

Description. Methods of describing a series of measurements on a group of individuals differ according to whether the variable measured is "continuous" or "discontinuous." A continuous variable is one that is manifested to any degree within a given range. These variables are sometimes spoken of as quantitative or representative, and their method of analysis as the statistics of measurement. Age, height, weight, blood pressure, strength of political beliefs and fondness for ice cream are of this type. They are most frequently described in the group by the arithmetic mean — the sum of all the individual measurements divided by the number of individuals in the group. Other values descriptive of series of continuous variables are the median — the value of that observation that has equal numbers of observations above and below it — and the mode — that measurement at which fall the greatest number of observations. A frequency curve is spoken of as bimodal when it appears that there are two separate points of increased frequency.

Discontinuous variables, on the other hand, are of the all-or-nothing variety. A patient is, usually at least, dead or not dead, male or female, has cancer or has not and so on. Alternative terms are qualitative or taxonomic variables, and their analysis is spoken of as the statistics of attributes. These variables are measured in the group by expression of the number of individuals in the group who exhibit the particular state as a proportion of the total population of the group.

It will be at once apparent that continuous variables may, by arbitrary classification, be transformed into discontinuous ones. For example, a series of individuals from birth to seventy years of age may be described by the percentages of the group falling into each of the age groups zero to nine, ten to nineteen and so forth. In practice both the mean and the percentage distribution should be used in the description of a series of continuous variables. The mean is a useful summarizing index, but it may be unduly influenced by a small number of very large or very small observations. Two series of quite different distribution may have closely similar means.

Description of variability. For discontinuous variables there is no problem in the description of variability. The only possible alternatives are that the attribute is present or absent in each individual, and in any series all the individual variation is summed up in the statement that so many per cent had the attribute and so many per cent had not.

For continuous variables, however, the mean is only a starting point in the description of the series, since it gives no indication of the "scatter" of individual values around it. A common practice is to give the "range" of the series, — that is, the highest and lowest values observed, — but this is unsatisfactory since it gives only the range including the rare and bizarre values. Of greater interest is the extent of the variation that is commonly seen. The statistical description of this variation is by the "standard deviation" of the mean, which is "the square root of the arithmetic average of the squares of the differences between the [individual] observations and their mean."[39] It is usually denoted by a $\pm$ sign after the statement of the mean. The variability within the series may then be rapidly assessed by the consideration that two thirds of the observations may be expected to lie within one standard deviation (plus or minus) of the mean, and 95 per cent within two standard deviations.

The mean and standard deviation form a satisfactory description of a series of values only if the distribution of the values is "normal." One of the important characteristics of a normal distribution is that the curve describing it is symmetric on either side of the mean. This is not always so. For instance, the distribution of a series of patients in duration of pregnancy as measured from the last menstrual period is not normal, since there are more pregnancies with gestations shorter than the mean of

forty weeks than there are with gestations greater than forty weeks.[40] Wootton, King and Smith[41] point out that many of the curves of distribution of biochemical values in healthy subjects are asymmetric and that, although the specification of variation in such values is of great clinical interest, the mean and standard deviation are unsuitable for the purpose. They describe a method of specifying such variation by assigning four levels for each biochemical test, the outer limits enclosing 98 per cent, and the inner limits 80 per cent, of the tested individuals. A value lying outside the outer limits is considered as probably abnormal. This method is useful in the circumstances, but it is cumbersome and not intended to replace the simpler standard deviation where this is appropriate.

Statistical significance. Much of statistical methodology is concerned with so-called tests of significance — that is, tests devised to determine the probability that the differences between compared observations are "real" and not the result of "chance." The concept of universal causation is now generally accepted, and it is recognized that, although the word "chance" occupies a useful place in popular parlance, there is in fact no such thing. However, for the present purpose, chance may be defined as the action of multiple, minor and independent factors acting without apparent design. Knowledge of the types and degrees of variation associated with such factors derives from study of the variation observed in such experiments as coin tossing and drawing differently colored but otherwise identical objects from containers. Tests of statistical significance are based on comparison of the differences noted in the experimental material with the differences that might be expected on the same numbers if the experiment had been of the coin-tossing type. For instance, in the comparison of the percentage death rates in two series, the hypothesis is set up that the two series are samples of the same wider population or universe. Under this so-called "null hypothesis," the difference between the percentage death rates should be no greater than could be accounted for by chance variation in the selection of the two samples. The difference expected on the chance hypothesis is then compared with the observed difference. The result is expressed in the form of a statement that the difference noted in the experimental material would have occurred on the average once in ten times in a coin-tossing experiment based on the same number of cases or, more briefly, that the probability that such a difference would have occurred by chance is one in ten or, more briefly still, p (probability) = 0.1.

If the probability that the difference between the two compared observations is due to chance is sufficiently remote the null hypothesis is discarded, and it is assumed that the two series are not in fact random samples of the same universe, but that they differ in some important respect. One commonly accepted standard of "statistical significance" is at the level of p equal to or less than 0.05 — it is regarded as dangerous to assume that a difference is real unless the probability of its being due to chance is 1 in 20 or smaller. This standard is a useful criterion, but its arbitrary nature should be remembered. As noted by Tippett[42] in this connection, there is no rational probability level at which possibility ceases and impossibility begins. The statement of the exact probability that the difference is due to chance is far preferable to the observation that a particular difference is or is not "significant."

For comparison of two means—percentages or proportions—the procedure outlined above involves the calculation of the standard error of the difference between the two compared measurements. For continuous variables the standard error of the difference between two means is dependent on the standard deviations of the means and of the numbers of cases in each series. Similarly, the standard error of the difference between two proportions is a function of the actual proportions and of the numbers of cases in the compared series. Formulas for the calculation of these figures may be found in any elementary textbook of medical statistics. The observed difference between the compared observations may then be divided by the standard error of the difference to obtain the "critical ratio." A difference equal to its standard error (critical ratio = 1) would occur on the average once in 3 times by chance. A difference twice its standard error (critical ratio = 2) lies on the border of conventional significance, occurring on the average once in 20 times by chance. A critical ratio of three indicates a difference that might be expected to occur by chance only once in 370 times.

The "t" test described by "Student,"[43,44] and encountered mostly in experimental work, may be used for the comparison of means when the number of observations is small. It involves only slight modification of the procedure described above, but is more accurate when the numbers of observations on which the means are based are less than thirty. White[45] gives a full description of this test, with illustrations of its use on physiologic data.

The chi-square (χ^2) test, developed by Pearson[46] involves a similar procedure. The test is used to compare two or more distributions. It may be used in the simple fourfold table in which each variable has only two groups, and also for situations in which there are multiple groupings — for instance, for comparing the distributions, in groups of 1 G., of the hemoglobin values noted in two series of subjects. As before, the null hypothesis is set up that these two distributions are random samples of the same universe. On this hypothesis the best estimate of the distribution of hemoglobin values within the theoretical universe is obtained by combination of the estimates of the two compared series. This best estimate is then used to find the expected distribution for each of the two series. χ^2 is the sum of the squared differences between observed and expected

values divided by the expected value in each cell. If the distributions are identical $\chi^2=0$, and the greater the difference between the two compared distributions, the greater χ^2. The probability that the difference between the two distributions is due to chance is read off from published tables[39,47] by the conjunction of the calculated χ^2 and a value known as the degrees of freedom ("n"), which depends on (but is not equal to) the number of cells in the compared distributions.

Correlation. The tests described in the preceding section may be used to determine whether or not there is a significant association between two variables or characteristics. They do not, however, tell anything about the extent of the association, since the significance of the differences depends not only on the size of the difference but also on the numbers of cases involved. For instance, the difference between a sex ratio (percentage of male births) of 51.48 noted in postwar years and the prewar figure of 51.42 was highly significant, not because of the magnitude of the difference but because of the extremely large number of births in the United States on which the figures were based.[48] When there are only two or three percentages to be compared, as in these sex ratios, there is little difficulty in assessing the extent of the association, since one can compare them directly. If, however, one wished to compare the sex ratios in twenty separate years there would be more difficulty in seeing at a glance the extent of any association between sex ratio and year. Similar difficulties arise in the determination of the association between two continuous variables. For instance, Putnam et al.[49] compared dietary intake of ascorbic acid with blood level. By grouping subjects according to mean daily intakes of 0.39 mg. or less and 40 mg. or more, and according to blood levels of under 0.6 mg. per 100 cc. and 0.6 mg. per 100 cc. or more, they found that those with high dietary intakes appeared significantly more frequently in the group with high blood levels than those with low dietary intakes. They noted, however, that this procedure gave no indication of the "firmness" of the association between the two variables. In such situations the coefficient of correlation ("r") is a useful index. Its rationale cannot be explained in the space now available, but several good descriptions are readily available.[50,51] Briefly, the correlation coefficient is a measure of the variability of the observations that is removed by assumption of a linear relation between the two correlated measurements. Its limits are from 0 to -1 for situations in which the correlation is inverse, and from 0 to $+1$ for positive correlations. When there is no correlation between the variables $r=0$ and when there is complete correlation — that is, a straight line could be fitted to all the points of observation — $r=-1$ or $+1$. Examples of the use of the correlation coefficient may be found in the work of Putnam and his associates[49] on ascorbic acid intake, Karn et al.[52] on infant birth weight and survival in siblings and Stocks[53] on regional differences in cancer mortality.

The standard error of a correlation coefficient can also be calculated, and a correlation is deemed significant if "r" is greater than twice its standard error. The latter can also be used for comparison of two correlation coefficients. It should be noted that the correlation coefficient does not accurately describe the completeness of associations that would be pictorially represented by a curve or any form other than a straight line.

The life-table method. The ordinary life table as used in vital statistics and by insurance companies is a type of visual aid in the expression of age-specific death rates in a population. The observed death rates are applied at each age interval to a theoretical population starting at birth with 100,000 or 1,000,000 members, to give the average number of the original population who would be expected to survive to given ages if the death rates currently observed continued to operate for the duration of life of the members of the theoretical population. From these data average expectations of life can be calculated for persons of a given age, again on the assumption of the continuation of current death rates.

The methodology of the life table can be applied to many studies of chronic disease. In such studies the "age" interval against which survival is measured may in fact be the chronologic age of the patients, as in studies of survival of children with congenital heart disease[54] or patients with diabetes.[55] On the other hand one may wish to date "age" from some occurrence other than birth — for instance, from the beginning of exposure to a toxic agent, or from the onset of a disease, as in Ipsen's[56] study of multiple sclerosis. Lastly, "age" may be dated from the time of receipt of treatment, and this procedure is particularly valuable in assessing the results of therapy in neoplastic disease. To date, however, it has not been as widely used for this purpose as it merits.

Similarly, for the alternatives of "death" or "continued survival," any other transformation of status, such as the onset of disease or the recurrence of manifest neoplasm, can be substituted. The table then becomes not a table of life but of life in a particular status — that is, disease free or recurrence free.

The most important advantage in the use of the life-table method in the study of the natural history or therapeutics of chronic disease is that the fullest possible use is made of all the data collected. In addition the results are expressed in a form that is readily comparable with other studies of the same problem, and, lastly, there is available a single summarizing index of the experience of the series — the mean expectation of life — although this is subject to the limitation that it gives no indication of variation in survival or death rates at different ages. Excellent and straightforward accounts of the technics of the life-table method for use in chronic-disease

studies have been given by Dorn[57] and Hill,[39] and Stocks[58] gives a comprehensive account of the method as used in the measurement of results of cancer therapy. Although not limited to discussion of this method of analysis articles of Densen,[59] Fix and Neyman[60] and Harris et al.[61] should also be read by those interested in follow-up studies.

Interpretation

Statistical analysis will assist in the interpretation of recorded data; unlike a supermarket calculator, it will not turn out an incontrovertible answer. Greenwood[62] gives an illustrative example. If, in a perfectly designed and executed therapeutic trial, statistical analysis of the difference in mortality experienced by the test and comparison groups indicated that such a difference would occur by chance only once in an average of a billion such trials, and if the treatment had some rational basis, one would suspect that the treatment was primarily responsible for the noted difference in mortality. If, however, the treatment had consisted of sticking postage stamps on the patients' bedsteads, unknown to the patients or attendants, the high degree of statistical significance would not influence one's reluctance to believe in the efficacy of the treatment.

In neglecting to take account of factors other than statistical significance errors of two kinds may arise: too great importance may be attached to statistical significance when it is present, or too little attention may be paid to observations that are not significant. Comments of Garrett[63] are pertinent to the first type of error, and the danger of the second has been stressed by Kennaway.[64] Just as high degrees of significance may result from the large number of cases involved, so may lack of significance result from too few observations rather than from the similarity of the compared groups. A difference that is not significant is nevertheless a difference. It should be interpreted with great caution, but may form a basis for further study.

The point made earlier regarding the desirability of giving the degree of significance is also relevant here, but statistical significance, even in high degree, should never be the sole criterion for the interpretation of observations. Equal consideration must be given to such questions as whether there is any trend in the observations and, if so, how regular it is, and whether the observations are internally consistent — for example, do they hold for males and females separately or for any other subdivisions that can be made of the data? In addition there are the biologic considerations pertinent to the particular problem under study, to which the statistical considerations must be quite secondary. It is of little benefit to demonstrate the statistical existence of the biologically absurd. Hill[65] has said, "the uninstructed . . . may be just as easily misled . . . by an appearance of 'mathematical' exactitude as by the simpler and more oldfashioned method of mishandling figures."

The valediction to this brief review is a plea that the practicing physician should not be deterred from the incorporation of statistical principles in his research studies by the apparent complexity of much of the statistical work published at present. There is little doubt that studies conducted without regard for elementary statistical principles suffer thereby, but this does not imply that the value of a study is in proportion to the complexity of the statistical technics used. Many delicate and ingenious statistical tests have been developed by workers in agriculture and experimental genetics. The philosophy underlying these tests is still the object of considerable statistical controversy,[66,67] but even if they are accepted as valid for the purpose for which they were devised, one must have considerable hesitation in applying them to the crude medical data that are presently collected. It is true that, in physiology and the other experimental basic sciences, sound data that justify delicate statistical tests are not unusual, and familiarity with these tests is of service to workers in these fields. But the predominant, and ultimately sole, concern of the clinician is the question of what *actually* happens to the patient, regardless of what might be expected to happen to him on the basis of *a priori* reasoning or of experimental evidence. As Asher[68] points out, too many treatments are still advocated merely because there is a theoretical reason why they *should* work, little attempt being made to find out whether they *do* work.

It is in this final and crucial stage in the structure of medical knowledge that collected data are crude—even more so for studies of the natural history of disease than for therapeutics. Those who apply delicate and complex statistical tests to such data frequently overlook the basic defects and biases of the data in their concern with the analysis. What have in the past been lacking and what are now urgently required are well planned and carefully collected data on man in all his aspects relevant to the prevention, detection and alleviation of disease. Interpretation of such data requires not detailed statistical knowledge but detailed knowledge of all aspects of the problem under investigation, a critical disposition, and acceptance and use of elementary statistical principles and technics.

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References

35. Yerushalmy, J. Statistical problems in assessing methods of medical diagnosis, with special reference to x-ray techniques. *Pub. Health Rep.* **62**:1432-1449, 1947.
36. Stocks, P. Measurement of public health. *Brit. M. Bull.* **7**:312-315, 1951.
37. Poynton, O. Death and distinction. *J.A.M.A.* **153**:1379, 1953.
38. Dedrick, C. L. Cultural differences and census concepts. *Milbank Mem. Fund Quart.* **27**:283-288, 1949.
39. Hill, A. B. *Principles of Medical Statistics.* Fourth edition. 252 pp. London: Lancet, 1948.

40. Gibson, J. R., and McKeown, T. Observations on all births (23,970) in Birmingham, 1947. I. Duration of gestation. *Brit. J. Social Med.* **4**:221-233, 1950.
41. Wootton, I. D. P., King, E. J., and Smith, J. M. Quantitative approach to hospital biochemistry: normal values and use of biochemical determinations for diagnosis and prognosis. *Brit. M. Bull.* **7**:307-311, 1951.
42. Tippett, L. H. C. *The Methods of Statistics: An introduction for workers in the biological sciences.* 222 pp. London: Williams and Norgate, 1931.
43. Student. Probable error of mean. *Biometrika* **6**:1-25, 1908.
44. Student. New tables for testing significance of observations. *Metron* **5** (No. 3):105-120, 1925.
45. White, C. Some examples of use of t-test on physiological data. *M. J. Australia* **2**:797-804, 1951.
46. Pearson, K. On criterion that given system of deviations from probable in case of correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *Philosophical Mag.* (series 5) **50**:157-175, 1900.
47. Fisher, R. A., and Yates, F. *Statistical Tables for Biological, Medical and Agricultural Research.* Third revised edition. Edinburgh & London: Oliver, 1943.
48. MacMahon, B., and Pugh, T. F. Sex ratio of white births in United States during the Second World War. *Am. J. Human Genet.* **6**:284-292, 1954.
49. Putnam, P., Milam, D. F., Anderson, R. K., Darby, W. J., and Mead, P. A. Statistical association between diet record of ascorbic acid intake and blood content of vitamin in surveyed populations. *Milbank Mem. Fund Quart.* **27**:355-391, 1949.
50. Treolar, A. E. *Biometric Analysis: An introduction.* 251 pp. Minneapolis: Burgess, 1951.
51. Croxton, F. E. *Elementary Statistics with Applications in Medicine.* 376 pp. New York: Prentice-Hall, 1953.
52. Karn, M. N., Lang-Brown, H., MacKenzie, H., and Penrose, L. S. Birth weight, gestation time and survival in sibs. *Ann. Eugenics* **15**:306-322, 1951.
53. Stocks, P. Regional and local differences in cancer death rates. In *Great Britain General-Registrar Office Studies on Medical and Population Subjects.* (No. 1.) 46 pp., 1947.
54. MacMahon, B., McKeown, T., and Record, R. G. Incidence and life expectation of children with congenital heart disease. *Brit. Heart J.* **15**:121-129, 1953.
55. Joslin, E. P., Dublin, L. I., and Marks, H. H. Studies in diabetes mellitus. VI. Mortality and longevity of diabetics. *Am. J. M. Sc.* **195**:596-608, 1938.
56. Ipsen, J., Jr. Life expectancy and probable disability in multiple sclerosis. *New Eng. J. Med.* **243**:909-913, 1950.
57. Dorn, H. F. Methods of analysis for follow-up studies. *Human Biol.* **22**:238-248, 1950.
58. Stocks, P. Methods of measuring results in treatment of cancer. *J. Fac. Radiologists* **1**:187-197, 1950.
59. Densen, P. M. Long-time follow-up in morbidity studies: definition of group to be studied. *Human Biol.* **22**:233-237, 1950.
60. Fix, E., and Neyman, J. Simple stochastic model of recovery, relapse, death and loss of patients. *Human Biol.* **23**:205-241, 1951.
61. Harris, T. E., Meier, P., and Tukey, J. W. Timing of distribution of events between observations: contribution to theory of follow-up studies. *Human Biol.* **22**:249-270, 1950.
62. Greenwood, M. Mr. Shaw on doctors. *Brit. M. J.* **2**:570, 1944.
63. Garrett, H. E. Mean differences and individual differences. *Human Biol.* **15**:166-170, 1943.
64. Kennaway, E. Statistical significance of biological data. *Brit. M. J.* **2**:663, 1954.
65. Hill, A. B. Statistics in medical curriculum? *Brit. M. J.* **2**: 366-368, 1947.
66. Hogben, L., and Wrighton, R. Statistical theory of prophylactic and therapeutic trials. I. Limitations of unique null hypothesis. *Brit. J. Social Med.* **6**:89-117, 1952.
67. Wrighton, R. F. Theoretical basis of therapeutic trial. *Acta genet.* (Basel) **4**:312-343, 1953.
68. Asher, R. Straight and crooked thinking in medicine. *Brit. M. J.* **2**:460-462, 1954.

MEDICAL INTELLIGENCE

TREATMENT OF HERPES ZOSTER WITH ACTH*

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HERPES zoster is usually a benign condition followed by spontaneous recovery. However, it may have serious complications when it occurs in elderly patients or when it involves the eye. There is no specific treatment. It is in older patients with extensive involvement, and in those with herpes zoster ophthalmicus, that innumerable remedies have been tried, with no relief of the excruciating pain in the acute stage of the disease and no prevention of serious complications and sequelae. For this reason, it seemed worth while to report on the successful treatment of herpes zoster with ACTH in 4 such patients. Other favorable reports on this form of treatment have recently appeared in the literature.

Nickel[1] administered 15 mg. of ACTH intramuscularly every six hours for four or five days to 18 patients with herpes zoster. Relief of pain was usually noted after the fourth or fifth injection and was complete and permanent in every case after five days of treatment. Weinstein and Lamas[2] reported excellent therapeutic results with the intravenous instillation of ACTH in 25 cases. Poulin[3] cited 3 cases of herpes zoster ophthalmicus in which ocular complications had developed during penicillin treatment and had failed to respond to cortisone administered topically and systemically. He injected 25 mg. of ACTH intramuscularly every six hours for five days. In all 3 patients the eye lesions improved dramatically within forty-eight hours. Steffensen[4] was equally enthusiastic.

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CASE REPORTS

CASE 1. A 70-year-old woman was admitted to the hospital on July 17, 1952, because of uncontrollable pain and increasing debility due to herpes zoster ophthalmicus. Despite the usual remedies her condition had become complicated by a severe uveitis and conjunctivitis. ACTH was given by intramuscular injection, 25 mg. 3 times a day for the 1st 2 days and 12.5 mg. 3 times a day for the 3d and 4th days. Dramatic relief occurred within 24 to 36 hours. The pain subsided and the uveitis and conjunctivitis cleared rapidly. There were no sequelae of corneal or intraocular complications; vision was not affected.

In this case ACTH appeared to accomplish in one day what ordinarily might have taken several weeks under conservative treatment. Too often this disease produces permanent damage to the various structures of the eye. Treatment to date has been disappointing. When ACTH became available it was turned to in desperation, and the results have been extremely gratifying.

CASE 2. A 58-year-old woman was admitted to the hospital on December 24, 1953, because of persistent agonizing pain due to thoracic herpes zoster. Treatment with vitamin B_{12}, thiamine, proteolytic enzyme, chlortetracycline and analgesics had failed to give relief. She had had diabetes for 10 years that was well controlled with a dietary

intake of 1500 calories and 15 units of protamine zinc insulin daily. On admission the fasting blood sugar was 116 mg., and the blood urea nitrogen 14.2 mg. per 100 cc. The pain had been present for 10 days, and the rash had appeared over the left lower axilla 4 days before admission; the lesions were in the vesicular stage. The diet of 1500 calories was continued, and crystalline zinc insulin administered in doses determined by the amount of sugar found in fractional samples of urine; 20 mg. of ACTH was injected intramuscularly every 8 hours for 3 days. The pain was relieved after 18 hours, and at the end of the 2d day the patient no longer complained of pain. Treatment was discontinued at the end of the 3d day, when the herpetic rash was dryer and paler, because of the danger of intensifying the diabetes with continued steroid therapy. During the 3 days of treatment the fasting blood sugar ranged from 115 to 145 mg. per 100 cc., and the fractional specimens of urine never showed more than 0.25 per cent of sugar; acetone did not appear in the urine at any time.

Because of the gluconeogenic effect of ACTH diabetes becomes temporarily intensified, and potential diabetes becomes overt; the insulin requirement of the patient becomes greater. One should be aware of this effect when considering giving the drug to diabetic persons. In this patient, as in others, the diabetes was easily controlled when the increased demand for insulin was met with the use of a short-acting insulin as dictated by the color reactions for sugar in fractional urine determinations. The short course of therapy necessary for relief further decreases the possibility of dangerous intensification of the diabetes.

Case 3. A 70-year-old man with chronic atrial fibrillation due to arteriosclerotic heart disease and long-standing hypertension had suffered bouts of congestive heart failure twice in the previous year. These episodes of moderate cardiac decompensation had responded quickly to digitalis, salt restriction and mercurial diuretics; he had been free of any symptoms of failure for 5 months. Herpes zoster appeared over the right lower thoracic cage at a time when he had not required any mercurial diuretics for 5 months, was restricting salt moderately and was taking 1 tablet of 0.25 mg. of a cardiac glycoside daily. The rash had been present for 9 days, and local applications of calamine, daily injections of 1000 microgm. of vitamin B_{12}, local x-ray therapy, a proteolytic enzyme and oxytetracycline had not relieved the persistent, intense pain and increasing exhaustion and weakness due to the inability to rest; 40 mg. of ACTH in a gelatin vehicle (to retard absorption of the drug and thus to prolong its action) was given daily by intramuscular injection for 5 days. During this therapy with ACTH the cardiac glycoside was continued in doses of 0.5 mg. daily by mouth, salt was rigidly restricted to less than 300 mg. daily, and 2 cc. of meralluride was given intramuscularly on the 2d and 4th days. Relief of pain was noticed by the end of 36 hours and was complete at the end of 3 days. The skin eruption did not progress, and there was no evidence of secondary infection. The patient did not manifest any degree of heart failure.

One should proceed more cautiously in patients with hypertension and cardiac disease. However, since ACTH therapy can usually be successfully concluded in three or four days, such clinical states as hypertension, atrial fibrillation and mild to moderate congestive heart failure are not absolute contraindications to the use of the hormone, particularly if scrupulous attention is accorded the hypertension or cardiac disease during the therapy.

Case 4. A 50-year-old woman was admitted to the hospital on May 16, 1952, for treatment of herpes zoster of the left lumbar and sciatic area. In 1950 a biopsy of a vertebra had shown multiple myeloma. X-ray therapy to the spine gave good relief. At the time of the present admission, she was free of any pain from the myeloma, and x-ray examination of the skull, spine and long bones yielded no evidence of gross osseous abnormality. The urine was negative for Bence-Jones protein on 8 occasions. The blood protein, sugar, urea nitrogen, alkaline phosphatase, calcium, phosphorus and sedimentation rate were normal. Except for a herpetic eruption on the left buttock, hip and thigh there were no remarkable physical findings; 25 mg. of ACTH was administered intravenously in 500 cc. of glucose in distilled water daily for 5 days, with good relief of the pain.

Case 5. A 74-year-old man was admitted to the hospital on March 10, 1954. He had become ill in February, with extensive herpes zoster of the right arm, chest and back. Although the lesions healed slowly, he gave a history of severe, constant intractable pain in the involved area since then. All modalities of therapy for herpes zoster, including a proteolytic enzyme, multiple smallpox vaccinations, daily intramuscular injections of 1000 microgm. of vitamin B_{12}, cobra venom, x-ray therapy and oxytetracycline, had been tried, with no relief of the pain. He was known to have had hypertension for 15 years; the blood pressure on admission was 230/110. An electrocardiogram revealed diffuse myocardial changes and right-bundle-branch block. He was admitted to the hospital for treatment with ACTH and for careful observation of any untoward effect of the steroid on his cardiovascular system. He was given 20 mg. intravenously in 500 cc. of glucose in distilled water daily for 2 days, and 25 mg. in similar fashion daily for 2 more days. There was no improvement in the pain of the postherpetic neuralgia. The blood pressure remained unchanged, and there was no evidence of heart failure or salt retention.

The failure in this patient is consistent with the experience of Nickel,[5] who also reported that ACTH did not prove valuable in postherpetic neuralgia. The hypertension and cardiac disease did not prevent the use of ACTH. There were no untoward effects from this short period of therapy with careful salt restriction.

Results of Treatment

Dramatic relief of pain occurred within twenty-four to thirty-six hours in 4 of the 5 subjects treated. The patient with postherpetic neuralgia failed to respond to therapy. The skin eruption did not progress in any case, nor was there any evidence of secondary infection. The course of healing of the superficial lesions continued in the usual manner, requiring one to three weeks. The uveitis and conjunctivitis that characterized the ophthalmic form of herpes zoster cleared rapidly. No complications or sequelae were observed. None of the usual signs of undesirable metabolic or physiologic disturbances, such as gain in weight, increased glycosuria, alkalosis (as measured by the carbon dioxide content of the blood) and hypopotassemia (as seen in the electrocardiogram), were present.

Discussion

It appears that a brief course of ACTH therapy is useful in the treatment of severe and extensive herpes zoster that has failed to respond to a variety

of agents. ACTH therapy shortens the acute phase, diminishes the intense pain and reduces the frequency of complications. The course of the pathologic process on the skin is unaltered, however. ACTH has not proved valuable in postherpetic neuralgia.[5] The hormone may be given by intramuscular injection, usually 25 mg. every four hours, by one or two intramuscular injections each day of 40 mg. in a gelatin vehicle, which retards absorption and prolongs the action of the drug, or by the daily intravenous administration of 25 mg. in 500 cc. of glucose in distilled water. The therapy is usually concluded in three to five days. The results are particularly rewarding in the ocular complications of herpes zoster ophthalmicus.

Because excellent therapeutic benefits can be obtained with a short course of parenteral administration there is no absolute contraindication to its use. One should proceed cautiously in patients with such clinical states as hypertension, cardiac disease, diabetes and ulcer. The last is probably a contraindication if therapy will extend for more than forty-eight hours. The emotionally disturbed patient should be watched carefully during treatment. In any case, if signs of intolerance develop, the drug should immediately be discontinued. Attempts should be made to obtain maximal suppression of the disease with the least possible amount of hormone.

Conclusions

A brief course of ACTH therapy is useful in herpes zoster. It should be reserved for patients in the older age group, those with herpes zoster ophthalmicus and those failing to respond to the conventional method.

References

1. Nickel, W. R. Herpes zoster treated with ACTH. *Arch. Dermat. & Syph.* **64**:372, 1951.
2. Weinstein, M., and Lamas, R. Tratamiento del herpes zoster con ACTH y cortisona. *Rev. méd. de Chile* **80**:266-269, 1952.
3. Poulin, J. E. Value of adrenocorticotropic hormone in herpes zoster ophthalmicus. *J. Maine M. A.* **43**:301-303, 1952.
4. Steffensen, E. H. Corticotropin, cortisone, and hydrocortisone in treatment of ocular disease. *J.A.M.A.* **150**:1660-1664, 1952.
5. *Current Therapy.* Edited by H. F. Conn. 835 pp. Philadelphia: Saunders, 1953. Pp. 559 and 560.

TORSION OF THE SPERMATIC CORD IN THE NEWBORN INFANT*

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TORSION of the spermatic cord in older children and young adults is a well known entity presenting a classic clinical picture with which most physicians are quite familiar. A fact that is not generally recognized is that the torsion may occur as an intrauterine phenomenon and thus present a clinical picture in the newborn infant quite different from that of torsion in older patients. Unless obstetricians and pediatricians recognize this syndrome and advise immediate surgery, atrophy of the involved testicle will invariably result.

A search of the literature reveals 5 previously reported cases of torsion of the spermatic cord within the first day of life, all treated by orchidectomy.[1-3] The purpose of this paper is to present 9 additional cases observed at the Children's Medical Center, Boston, during the fifteen-year period 1940-1955.

Etiology and Pathology

Much has been written about the etiology and pathology of torsion of the spermatic cord in older patients. As pointed out by Campbell[1] the pathology of the condition in the newborn infant is quite different. In older patients the site of torsion is within the tunica vaginalis, whereas in the newborn infant the twist occurs outside the tunica vaginalis. This was true in all our cases. The importance of this observation is a moot point, but it suggests that intrauterine torsion is of a different etiology. In none of our cases have we noted any anatomic anomaly of the testicle or its attached structures as is frequently seen in older patients.[1]

Clinical Findings

In all our cases the baby was found at birth to have an enlarged, firm, reddish or purple, nontender mass in the scrotum that did not transilluminate. None of these babies presented gastrointestinal disturbances such as vomiting and refusal of feedings. Systemic manifestations were minimal, with little or no fever or signs of toxicity. Pain was not a notable factor, and the mass did not seem to be tender.

In several earlier cases a diagnosis of tumor was entertained. We have not, however, encountered a testicular tumor (such as an embryoma or a teratoma) in a newborn infant. Likewise, we have not seen orchitis, epididymitis, torsion of the appendix testis or strangulated inguinal hernia at the time of delivery.

The diagnosis of torsion is therefore strongly suggested by the finding of an enlarged, firm, nontender, discolored (reddish or purple) scrotal mass that does not transilluminate. The clinical findings in the 9 reported cases are summarized in Table 1.

Treatment

The treatment should consist of immediate surgical exploration, with reduction of the torsion. Unfortunately, many patients are treated with ice caps and antibiotics in the vain hope that the swelling will subside. If surgery is delayed beyond the first

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day of life, some degree of atrophy of the involved testicle will almost invariably result.

Regardless of the gross appearance of the involved testicle, orchidectomy should not be carried out unless there is evidence of systemic toxicity. No complications have been observed when a testicle that grossly appeared black and apparently necrotic was left in place; furthermore, the degree of subsequent atrophy in such cases may be surprisingly minimal. Although some atrophy may result, it is conceivable that the testis may retain some degree of endocrine activity.

Routine exploration of the opposite testicle was not practiced in this group of patients. None have subsequently manifested testicular torsion on the opposite side. Since, pathologically, intra-uterine torsion appears to be a different phenomenon from torsion in older patients and is not associated with testicular anomalies, one would question the advisability of such a procedure. Table 2 summarizes the results of treatment in this series.

TABLE 1. *Clinical Findings.*

CASE NO.	AGE WHEN TORSION FIRST NOTED	PAIN	TENDERNESS	VOMITING	FEVER	SIDE AFFECTED	ENLARGEMENT OF TESTICLE	CONSISTENCE OF SCROTAL MASS	COLOR OF SCROTAL MASS	TRANSILLUMINATION	SYSTEMIC TOXICITY
1	Birth	Absent	Absent	Absent	Absent	Left	Twice normal size	Extremely hard	Purple	Absent	Absent
2	Birth	Absent	Absent	Not recorded	Present*	Left	Thrice normal size	Hard	("Discolored")	Not recorded	Moderate
3	Birth	Absent	Absent	Absent	Absent	Right	2½ times normal size	Hard	Purple	Absent	Absent
4	Birth	Absent	Absent	Absent	Absent	Right	Thrice normal size	Hard	Bluish	Absent	Absent
5	Birth	Absent	Absent	Absent	Absent	Left	Twice normal size	Hard	Bluish	Absent	Absent
6	Birth	Absent	Absent	Absent	Absent	Left	Thrice normal size	Stony hard	Bluish	Absent	Absent
7	Birth	Absent	Absent	Absent	Absent	Left	4 times normal size	Stony hard	Bluish	Absent	Absent
8	Birth	Absent	Absent	Absent	Absent	Right	Thrice normal size	Stony hard	Reddish	Absent	Absent
9	Birth	Absent	Absent	Absent	Absent	Left	1½ times normal size	Firm	Reddish	Absent	Absent

*Temperature of 101°F. by rectum.

TABLE 2. *Results of Treatment.*

CASE NO.	AGE AT OPERATION	TYPE OF OPERATION	GROSS APPEARANCE OF TESTICLE	SUBSEQUENT ATROPHY
1	1 mo.	Orchidectomy	Bluish black	—
2	6 wk.	Orchidectomy	Infarcted	—
3	3 days	Reduction	Gangrenous	Moderate
4	5 days	Reduction	Completely infarcted	Moderate
5	3 days	Reduction	Reddish black	Complete
6	4 days	Reduction	Necrotic	None
7	5 days	Reduction	Black	Moderate
8	2 days	Reduction	Reddish black	Moderate
9	5 days	Reduction	Bluish black	Minimal

CASE REPORTS

CASE 1. P.M. (C.H. 284227), a 1-month-old infant, was admitted to the hospital on June 27, 1944. He was referred to the Surgical Service because of the finding of a mass in the left scrotum. This had been noted at the time of delivery but had been considered an insignificant finding. There had been no variation in size and no symptoms related to the mass. Examination revealed the mass to be firm, round, nontender and somewhat fixed to the scrotal skin, which presented a bluish discoloration. It did not transilluminate. A radical orchidectomy was performed because of a preoperative diagnosis of testicular tumor. The pathological report was infarction of testis secondary to torsion of the spermatic cord.

CASE 2. R.K. (C.H. 283991), a 6-week-old infant, was admitted to the hospital on July 1, 1944, because of an enlarged left testicle first noted at birth. There had been no symptoms or appreciable increase in size. On examination the left testicle was 3 times the size of the right and quite firm, and the overlying skin was somewhat discolored. At operation the surgeon could not be certain whether the tremendously discolored, edematous mass represented a neoplasm or infarction secondary to a torsion. A total orchidectomy was performed. Examination of the surgical specimen revealed hemorrhagic infarction secondary to a torsion.

CASE 3. J.Y. (C.H. 292439), a 3-day-old infant, was admitted to the hospital because of an enlarged right testicle, which had been noted at the time of delivery and had not changed since. On examination the left testicle was undescended but could be palpated at the internal ring. The right testicle, which was 2½ times the normal size and quite firm, did not transmit light. There was a purple discoloration of the overlying scrotal skin. At operation the testicle was found to be infarcted and bluish black secondary to a torsion with 2 complete turns of the cord structures midway between the external inguinal ring and the testicle. The torsion was reduced, a testicular biopsy obtained, and the testicle returned to the scrotum. The pathological report was "infarction of the testicle with no evidence of tumor." When the patient was last seen 7 months later the testicle was firm in consistence and of approximately normal size.

CASE 4. D.R. (C.H. 338738), a 4-day-old infant, was admitted to the hospital because of an enlarged right testicle noted at the time of birth. On examination the testicle was 3 times the normal size, firm and nontender. The overlying skin presented a bluish discoloration. The mass did not transilluminate. Exploration revealed a 360° torsion of the spermatic cord between the external ring and the tunica vaginalis. The testicle itself was quite dark, hemorrhagic and infarcted. It was the opinion of the operating surgeon that no living cells were left in the testicle; nevertheless, it was left in place.

CASE 5. W.L. (C.H. 342349), a 2-day-old infant, was admitted to the hospital because of an enlarged left testicle. At birth the testicle had been noted to be somewhat enlarged; after 24 hours it assumed an obvious bluish discoloration. Operation revealed a complete 360° torsion of the spermatic cord in the region of the external ring. The torsion was reduced, and the tunica albuginea incised because of testicular edema and reddish-black discoloration. On examination 2 years later the left testicle was atrophic.

CASE 6. P.S. (C.H. 387329), a 3-day-old infant, was admitted to the hospital because of a mass in the left scrotum present since birth. The left testicle was 3 times the normal size, nontender and stony hard, and the overlying skin presented a bluish discoloration. The mass did not transilluminate. Operation revealed a torsion of the spermatic cord between the external ring and the tunica vaginalis. The torsion was reduced. The testicle was noted to be quite small and appeared necrotic. A biopsy was taken and subsequently reported as showing infarction of the testicle. The testicle was left in place in spite of its necrotic appearance. When examined 2 years later the left testicle was normal in size and consistence.

CASE 7. K.D. (C.H. 431006), a 5-day-old infant, was admitted to the hospital because of an enlarged left testicle first noted at the time of delivery. The testicle was stony hard and 4 times the normal size, and the overlying skin was discolored and reddened. Operation was carried out on the day of admission, and a 360° clockwise torsion of the spermatic cord just superior to the tunica vaginalis was encountered and reduced. The entire testicle appeared black and gangrenous. On incision of the tunica albuginea the parenchyma of the testicle appeared black and nonviable. After reduction of the torsion no improvement in the color of the testicle could be detected. The testicle was left in place.

CASE 8. S.D. (C.H. 412648), a 2-day-old infant, was admitted to the hospital because of an enlarged right testicle first noted at the time of birth. A hydrocele was observed on the left side. The right testicle was 3 times the normal size and stony hard, and the overlying skin presented a reddish-bluish discoloration. At operation the testicle was markedly discolored, infarcted and probably nonviable because of a torsion of the spermatic cord just outside the tunica vaginalis. The torsion was reduced, and the tunica albuginea incised. When the patient was last seen 6 months later the right testicle was atrophic.

CASE 9. M.C. (C.H. 418238), a 2-day-old infant, was admitted to the hospital because of an enlarged left testicle noted at the time of birth. Examination revealed the left testicle to be firm to palpation, enlarged and adherent to overlying skin. At operation a 360° torsion outside the tunica vaginalis was identified and reduced. The testicle itself was gangrenous, and, on incision, considerable blood clot was evacuated. The testicle was returned to its normal position. On last examination 6 weeks later, the testicle was smaller than normal and was quite firm.

SUMMARY

Attention is called to torsion of the spermatic cord in the newborn infant. Nine cases are reported; the pathology and clinical findings are discussed and compared with those of torsion of the testicle in older patients.

The classic clinical picture generally should leave little doubt of the diagnosis.

The treatment should consist of immediate surgical exploration during the first day of life. Orchidectomy should not be done unless the patient demonstrates findings of systemic toxicity. Although partial atrophy may result we believe that the testicle may retain some degree of endocrine activity.

REFERENCES

1. Campbell, M. F. Torsion of spermatic cord in newborn infant. *J. Pediat.* **33**:323-327, 1948.
2. Biorn, C. L., and Davis, J. H. Torsion of spermatic cord in newborn. *J.A.M.A.* **145**:1236-1238, 1951.
3. Taylor, M. R. Case of testicle strangulated at birth: castration: recovery. *Brit. M. J.* **1**:458, 1897. Cited by Campbell[1] and Biorn and Davis.[2]

CASE RECORDS
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CASE 41421

PRESENTATION OF CASE

A forty-two-year-old man was referred to the hospital for evaluation of a rounded density discovered on a roentgenogram from a routine survey of the chest.

The patient was asymptomatic except for occasional transitory episodes of burning pain in the anterior chest that were associated with inspiration but were unrelated to exercise, emotional stress or coughing.

There was known hypertension of thirteen years' duration, which was initially discovered in the course of an insurance examination. On various occasions in the years before admission the blood pressure ranged from 200 systolic, 125 diastolic, to 156 systolic, 104 diastolic. Six years before admission the patient was followed for several months in the Hypertension Clinic. He was essentially asymptomatic at the time, but showed evidence of slight enlargement of the left ventricle in the x-ray film and electrocardiogram. He was treated conservatively and placed on a low-salt diet. There were no visual disturbances, headaches, symptoms of heart failure or paroxysmal attacks. Sympathectomy was being considered, but the patient did not return to the clinic.

Of 5 siblings, 1 brother had died of "hypertension" a year after a sympathectomy, and 1 brother and 1 sister had died of "Bright's disease" in childhood.

Physical examination showed a nervous man in no distress. The fundi revealed some arterial spasm without arteriovenous nicking, hemorrhage or exudate. The lungs were clear to percussion and auscultation. The left heart border was percussed 2 cm. to the left of the midclavicular line. There was a Grade 3 systolic murmur that was heard loudest just above the aortic area and was transmitted to the neck vessels. A very faint systolic murmur was heard just medial to the left scapula. The abdomen was normal. Two observers felt equal pulses in the lower extremities; two others were unable to palpate dorsalis pedis, posterior tibial or popliteal pulsations and believed that the femoral pulses were decreased. The blood-pressure sounds in the legs were faintly heard at 130 systolic, 100 diastolic.

The temperature was 98°F., the pulse 90, and the respirations 20. The blood pressure was 200 systolic, 130 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11.0 gm. per 100 cc. and a white-cell count of 9600. A blood Hinton test was negative. The prothrombin time was 13.5 seconds (normal, 13 seconds). The nonprotein nitrogen was 37 mg., and the total protein 7.4 gm. per 100 cc. The twenty-four-hour urinary creatinine content was 14 mg. per kilogram of body weight (normal, 15 to 25 mg. per kilogram). The phenolsulfonphthalein excretion was 25 per cent in fifteen minutes and 70 per cent in two hours. Only moderate pressor responses to 0.025 mg. and 0.05 mg. of histamine were obtained. These were poorly counteracted by a 5-mg. dose of Regitine. An electrocardiogram showed a left-bundle-branch block. An x-ray film of the chest demonstrated a heart of normal size, a "somewhat rounded" left ventricle, a "slightly elongated aorta" and a rounded area of density extending from the upper mediastinum to the left apex (Fig. 1). Films of the ribs showed notching of the upper mid-dorsal ribs posteriorly. An intravenous pyelogram was normal.

On the sixth hospital day an operation was performed.

FIGURE 1. *Posteroanterior View of the Chest. There is notching of the inferior aspects of several of the ribs posteriorly in the midthoracic region (white arrows). A round mass lies to the left of the upper thoracic spine, projecting within the apex of the lung (black arrows).*

Differential Diagnosis

Dr. Allan L. Friedlich*: The discussion of this patient centers around two problems, the hypertension and the mass in the chest. It is perfectly clear that the patient had coarctation of the aorta with "all the trimmings." He had asymptomatic hypertension so that we do not know how long the blood pressure was elevated, but we do know that he had hypertension at the age of twenty-nine. At that time, a few years after coarctation of the aorta had become one of the few curable causes of hypertension, the diagnosis was missed in the Hypertension Clinic. This, I think, deserves some comment. It is easy to miss the diagnosis of coarctation, and the diagnosis will continue to be missed until we keep in mind that it can be excluded only in one way — that is, by demonstrating that the systolic blood pressure in the legs is higher than that in the right arm. The diagnosis of coarctation rests on the cardinal finding of a lower blood pressure in the legs than in the right arm. It is important to remember that it is not possible to rely on the presence of good femoral pulses to rule out the presence of coarctation. Occasional patients are seen in whom the leg pulsations are of essentially normal amplitude and in whom coarctation of a high degree exists. Until we make it a rule to take the blood pressure in the legs of all hypertensive patients, particularly in young patients, and in all children who have a murmur of obscure origin, we shall miss a few cases of coarctation. In this connection we must remember that the range of normal blood pressure is lower in children than it is in adults. Cases have been missed because a blood pressure of 135 systolic, 80 diastolic, in a young child was erroneously considered normal. Rarely, one sees a patient in whom the blood pressure is normal at rest but rises sharply with exercise as a result of an increase in the cardiac output.

This man had a blood pressure of 200 systolic, 130 diastolic, in one of the arms; which arm is not specified.

Dr. Benjamin Castleman: According to one of the notes in the record the blood pressure in the left arm when the patient was sitting was 200 systolic, 120 to 130 diastolic, and the blood pressure in the legs was faintly obtained at 130 systolic, 100 diastolic, bilaterally.

Dr. Friedlich: If the left subclavian artery is involved in the coarctation, this fact is important for the surgeon to know. If it is, one will find hypertension in the right arm and a distinctly lower blood pressure in the left arm because of the inclusion of the left subclavian artery in the coarcted segment of the aorta. Rarely, an anomalous right subclavian artery may arise below the area of coarctation and cross behind the esophagus. In such a case the blood pressure may be low in the right arm and high in the left. I think we can rule this out on the basis of the x-ray findings.

The blood-pressure differences of which we have spoken indicate an aortic block. This patient was in the age group in which thrombosis of the lower end of the aorta may be seen. Most patients with thrombosis of the lower aorta complain of claudication. In the absence of any notation of claudication, we will assume that it was absent in this man.

Several points indicate that this was a block in the thoracic aorta due to coarctation. In addition to hypertension, he had a systolic murmur maximal over the base of the heart that was entirely compatible with coarctation. The fact that the murmur was heard in the back is another clue. The more important evidences of coarctation will be seen in the x-ray films. The laboratory data need little discussion; they indicate good renal function without evidence of unilateral renal disease and no evidence of pheochromocytoma. Although pheochromocytoma in the chest has been described, I think that the simultaneous occurrence of such a tumor with coarctation would be too extraordinary to accept.

This man was forty-two years old. By and large, surgeons prefer to operate on this condition in persons below the age of thirty. A number of patients in the older age group have had a resection of the coarctation, but the risk is increased by the loss of elasticity of the aorta and by another factor, which I shall mention later. Now that aortic grafts are readily available it is possible to operate on older patients with less trepidation since, if the two ends of the aorta cannot be joined after excision of the coarctation, a graft may be used to bridge the gap.

The second and more crucial problem is the nature of the mass in the chest. I think this may be a good time for Dr. Reeves to show the x-ray films.

Dr. John D. Reeves: On the posteroanterior films taken seven years before admission one can see the presence of erosion or notching of the lower margin of the ribs bilaterally. There is the mass in the left superior portion of the mediastinum. On admission the mass has enlarged slightly (Fig. 1). In the lateral film the mass is seen not to be in the anterior or middle mediastinum, and in the right anterior oblique view it lies paravertebrally in the superior mediastinum. In the posteroanterior projection one can well see that the path of the esophagus does not take its usual course to the left. In the upper mediastinum it drops straight downward. There is some indentation due to the aortic impression and a small point of barium beneath the aortic arch. In the left anterior oblique view, there is minimal displacement of the esophagus just below the level of the arch. This displacement is to the right and anteriorly. The left main bronchus, of course, is beneath that.

Dr. Friedlich: Do these findings in the esophagus and the appearance of the lower portion of the

*Assistant physician, Massachusetts General Hospital.

aorta really constitute visualization of the coarctation?

DR. REEVES: The actual coarctation, the indentation of the aorta, is not seen. Many of the accessory signs are present — the notching of the rib, the straight drop of the esophagus, indicating perhaps some enlargement of the great vessels and the deviation of the esophagus below the aortic arch, which suggests a mass posteriorly.

DR. FRIEDLICH: Could this be a poststenotic dilatation of the aorta below the coarctation?

DR. REEVES: Yes.

DR. FRIEDLICH: Various people, including Robbins and Wyman,[1] have pointed out that the coarctation itself can frequently be seen in a plain film, particularly with the aid of a barium swallow. This is of particular value in children who have not had time to develop notching of the ribs.

If the mass in the left apex was a tumor it must have been a benign one since it was present eight years before admission. The various benign tumors of the chest could be enumerated, but the location and nature of this mass make it statistically most likely to have been neurofibroma. This patient, however, had coarctation of the aorta. One of the factors that increase the risk of surgery in older patients with coarctation is the occasional presence of aneurysms of the intercostal arteries. These arteries serve as collateral circulation around the aortic obstruction. They therefore become dilated and tortuous, producing notching of the ribs and in older patients sometimes even aneurysmal dilatation. Such aneurysms are thin walled, are friable and constitute a hazard because bleeding from them is difficult to control. For this reason some of the patients in the older age group operated on here for coarctation have been given hypotensive spinal anesthesia.

It must be rare for an intercostal aneurysm to present as a tumor of the lung. I believe, however, that Dr. Richard H. Sweet spoke of such a case, which he had encountered a few years ago. In the absence of visible pulsation of this mass on fluoroscopic examination, the only way to differentiate a benign tumor from an aneurysm with certainty is by means of angiography. In the absence of such evidence, I should assume that this was an aneurysm of an intercostal artery, complicating coarctation of the aorta.

DR. JOHN D. STOECKLE: I should like to know if the aneurysms occur in any particular positions; are they paravertebral or not? Are they in the posterior mediastinum?

DR. FRIEDLICH: The aneurysms usually occur close to the aorta, where the intercostal arteries empty into the aorta below the coarctation.

CLINICAL DIAGNOSIS

Neurofibroma in mediastinum.

DR. ALLAN L. FRIEDLICH'S DIAGNOSES

Aneurysm of intercostal artery.
Coarctation of aorta.

ANATOMICAL DIAGNOSES

Aneurysm of intercostal artery.
Coarctation of aorta.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: As Dr. Friedlich stated, this patient had been followed in the Hypertension Clinic for years and was finally sent into the hospital to have a posterior mediastinal neurofibroma removed. One of the medical residents, Dr. Joseph J. Barlow, who saw the patient to determine whether he was a good operative risk, took the blood pressure in the legs and suggested the diagnosis of coarctation of the aorta. He then examined the x-ray films and saw the notching of the ribs.

DR. REEVES: We suggested an angiocardiogram.

DR. CASTLEMAN: At operation the surgeon was able to feel the mass and removed it. It turned out to be an aneurysm, as Dr. Friedlich predicted. The aneurysm was quite large, measuring about 2.5 cm. in diameter. It was thick walled and fibrous, and microscopically there was fibrous proliferation of the intima with marked arteriosclerosis with cholesterol crystals. The intima, in places, was calcified. The aneurysm did not contain a thrombus. I think, if an angiocardiogram had been taken, the aneurysm would easily have been seen.

Dr. Friedlich, you made it appear that not infrequently a good-sized aneurysm is found with coarctation. I had not realized it was so common.

DR. FRIEDLICH: Perhaps I was misleading. Small aneurysms in older adults are relatively common. An aneurysm of sufficient size to masquerade as a tumor of the lung must be rare.

DR. CASTLEMAN: The severe arteriosclerosis in the aneurysm suggests that the aneurysm had been present for a long time.

DR. STOECKLE: Was it the intercostal artery?

DR. GILES TOLL: I believe that Dr. Robert C. Coe's impression was that the aneurysm was of the second intercostal artery. As Dr. Friedlich has indicated, it was extremely difficult for us to remove. It would have been definitely better if the operation had been performed under hypotensive spinal anesthesia.

DR. CASTLEMAN: The patient has got along well and, I believe, is planning to come in for removal of the coarctation.

DR. TOLL: That is still a question. He is over forty, is in good condition and does not have any significant symptoms. The aorta was quite arteriosclerotic. We are deliberating whether we shall operate or treat him in the Hypertension Clinic.

DR. FRIEDLICH: The hypertension was quite severe.

DR. CASTLEMAN: Would you advise removing the coarctation?

DR. FRIEDLICH: I should like to see him before making such a decision.

DR. REEVES: In the literature on radiology[2] there are many reports of aneurysms of the proximal collateral vessels in coarctation, particularly of the intercostal, internal mammary and subclavian arteries and those in the circle of Willis. Occasionally, vertebral aneurysms have produced compression of the cord, and one aneurysm produced compression of the bronchus. Dissecting aneurysm of the aorta is common.[3] This is suggested by some physicians to be due to degeneration of the medial arterial layer.

One condition that has been reported, which I can find very little about, is that the ovaries are occasionally absent with coarctation. Do you know anything about that?

DR. FRIEDLICH: Coarctation is much less common in women than in men. Women with ovarian agenesis are an exception to this.

DR. PHILIP H. HENNEMAN: Coarctation of the aorta is more common in males and in patients with ovarian agenesis. This apparent paradox is partially explained by the recent finding that most patients with ovarian agenesis have nuclear chromosomal patterns characteristic of the male sex and are "genetic males." Apparently, absence of the testes does not permit fetal development of the wolffian system into male genitalia; in the absence of the gonads the müllerian system persists, giving rise to the female genital system. Thus, "genetic males," if lacking in testes, may appear to be females. It appears that such "genetic males" may still have the anomalies and defects more often associated with males than with females.[4]

REFERENCES

1. Robbins, L. L., and Wyman, S. M. Coarctation of thoracic aorta: signs demonstrable by conventional roentgenography. *New Eng. J. Med.* **248**:747-752, 1953.
2. *Text-book of X-Ray Diagnosis.* Edited by S. C. Shanks and P. Kerley. Vol. 2. Philadelphia: Saunders, 1951. Pp. 94-100.
3. *Pathology.* Edited by W. A. D. Anderson. 1453 pp. St. Louis: Mosby, 1948. P. 565.
4. Grumbach, M. M., Van Wyck, J. J., and Wilkins, L. Congenital gonadal dysgenesis, ovarian agenesis, and male pseudohermaphroditism: relationship to theories of human sex differentiation. *J. Clin. Endocrinol.* **15**:845, 1955.

CASE 41422

PRESENTATION OF CASE

First admission. A ten-year-old girl entered the hospital because of pain in the left thigh.

Seven months before admission she received a Pogo stick for her birthday. After jumping actively for one week, she noted the onset of dull aching pain in the left thigh when she crossed her legs. Soon thereafter the pain appeared at night and after standing for long periods. The pain was situated in the left anterior and lateral portions of the thigh; it occasionally extended below the knee. It was aggravated by activity and relieved by aspirin, which the patient began to take every night. X-ray films taken five and three months before admission were said to be normal. A few months before admission the pain became more severe. There were no constitutional symptoms or pains elsewhere.

The past history was noncontributory.

Physical examination was negative except for findings referable to the left lower extremity. The patient stood and walked with the left hip slightly adducted. There was some limitation of motion of the left hip on both internal and external rotation. There was no muscle or joint tenderness. A Trendelenburg test was negative. The left knee and ankle jerks were decreased and there was slight weakness of the left hamstring muscles.

The temperature was 99°F., the pulse 103, and the respirations 21. The blood pressure was 110 systolic, 78 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 cc., a white-cell count of 7600, with 61 per cent neutrophils, 33 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophils and a sedimentation rate of 22 mm. per hour. The total protein was 8.7 gm., the calcium 9.6 mg., the phosphorus 4.4 mg., and the alkaline phosphatase 7.8 units per 100 cc. An electromyogram of the muscles of the left thigh and calf was normal. An old-tuberculin test in a dilution of 1:100 was negative in forty-eight hours. X-ray films of the lumbosacral spine, hips, femurs and tibias were normal except for the presence of a mild to moderate amount of osteoporosis about the left hip. The patient was given crutches and discharged on a program of exercise.

Second admission (eight months later). In the interval since the first admission the patient continued to have episodes of pain in the left hip after activity. Shortly before admission the pain began to increase in severity. On physical examination the left thigh was now 1 cm. less in circumference than the right. There was a 15° flexion deformity of the left hip, with considerable limitation of external rotation and absence of internal rotation. This limitation was present in both flexion and extension. There were no nodules or rash.

The temperature was 100°F., the pulse 105, and the respirations 21.

Examination of the urine was negative. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc., a white-cell count of 9300, with 60 per cent neutrophils, 28 per cent lymphocytes, 4 per cent monocytes and 8 per cent eosinophils, and a sedimentation rate of 0.72 mm. per minute corrected. The calcium was 10 mg. per 100 cc.; the phosphorus was 4.3 mg. and the alkaline phosphatase 8.1 units

per 100 cc. X-ray films revealed greater osteoporosis of the left hip than on the previous examination. There was widening of the joint space. A poorly defined radiolucent zone, 1-cm. in diameter, was present in the proximal portion of the left femoral neck (Fig. 1). The calcar femorale showed striations that were not visible on the previous films; 4 cc. of synovial fluid aspirated from the left hip joint was slightly cloudy and formed a clot immediately. The mucin formed a tight clot with acid (Type 1). The red-cell count was 2050, and the white-cell count 1650 per cubic millimeter, with 30 per cent neutrophils, 16 per cent lymphocytes and 54 per cent monocytes. The sugar was 194 mg. per 100 cc. Culture revealed no growth.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Joel C. Goldthwait*: This ten-year-old girl had a history and physical findings of disease of the left hip that gradually progressed over a period of fifteen months. The findings are not typical of any infectious, rheumatoid or neoplastic process that I can recall. There were borderline signs of systemic reaction — namely, slight elevation of temperature and pulse. To define the disease of the left hip accurately from the purely clinical point of view is impossible; therefore, we must turn to the x-ray and laboratory data for help. There were four x-ray examinations in the second, fourth, seventh and fifteenth months of the disease. We are told in the protocol that these showed a gradually developing osteoporosis, with final appearance of a radiolucent area in the femoral neck. In the last examination there was some widening of the joint space, presumably because of either fluid or soft-tissue enlargement in the space, and striations were made out in the calcar femorale. I wonder whether we may see the films.

Dr. C. C. Wang: The examination of the chest is negative. The films of the pelvis, including both hips, taken on the first admission show nothing strikingly abnormal. There may be slight demineralization of the proximal portion of the left femur, but this observation is not definite. The films taken on the second admission, approximately eight months later, show an area of poorly defined rarefaction in the left hip without any adjacent bony sclerosis. This lesion measures approximately 1 cm. in diameter (Fig. 1). On the stereoscopic films one can see that the osteolytic area lies anteriorly along the intertrochanteric line. The joint capsule appears bulged laterally as compared with the right. The skeletal examination shows no osteolytic lesions elsewhere in the bones. We do not have a skull film.

Dr. Goldthwait: The finding in the x-ray film of bulging of the capsule with a lesion in the bone so far away from the joint adds to the confusion. I suppose that the findings could fit with an infectious, a rheumatoid or even a neoplastic process in the joint, which conceivably could appear first as osteoporosis of the neighboring bone—although the observation that there was osteoporosis is not as certain as was implied by the statement in the protocol. It is difficult to conceive of a neoplastic lesion primary in bone, with a fifteen-month interval between the onset of symptoms and the appearance of a discrete bone lesion and an eight-month interval between the appearance of osteoporosis and the appearance of a discrete lesion. This is possible but unlikely. The x-ray appearance is not that of any of the common bone tumors, although one should consider lesions such as osteoid osteoma, hemangioma and Ewing's tumor. Because of the apparent involvement of the joint and the time relation I am going to rule out arbitrarily for the time being primary neoplasm in bone. Also, by the same line of reasoning, I can rule out an infectious process primary in bone. Osteomyelitis can be eliminated by the fact that a discrete lesion appeared in bone only after eighteen months.

Figure 1. *Anteroposterior View of the Left Hip.*
A 1-cm. area of rarefaction is present at the base of the femoral neck. There is moderate osteoporosis and minimal reactive change along the calcar femorale.

*Visiting physician, Robert Breck Brigham Hospital.

One other group of conditions to be considered is the histiocytoses, — Gaucher's disease, Niemann–Pick disease and eosinophilic granuloma, — but I should expect more evidence of localized bone disease in the x-ray films with the amount of symptoms and the amount of joint limitation that the patient had.

The laboratory data are not helpful generally. The routine blood and urine examinations were negative except for the findings of 5 and 8 per cent eosinophils on the two admissions. The sedimentation rate was slightly elevated on the first admission and definitely so on the second. The alkaline phosphatase was somewhat high, but I think perfectly all right for a child of this age. The negative tuberculin test, 1:100, was quite strong evidence against a tuberculous process in a child.

Was this tuberculosis of the hip joint? The clinical and x-ray pictures are consistent with this diagnosis, but the negative tuberculin test and the findings in the joint fluid — the low white-cell count, the low percentage of neutrophils and the clumped mucin precipitate in the synovial fluid — are against it. The high sugar of 194 mg. per 100 cc. might lead one to believe that the child was diabetic. Do you have a blood sugar that I can compare with it?

Dr. Benjamin Castleman: The blood sugar was 203 mg. per 100 cc.

Dr. Evan Calkins: The sugar values were determined at the time of the operation when the patient was under ether anesthesia; I think this accounted for the elevated value.

Dr. Goldthwait: Was the fluid examined for acid-fast bacilli?

Dr. Castleman: Yes; no acid-fast bacilli were found.

Dr. Calkins: A guinea pig was inoculated, but it is too early yet to know what it will show.

Dr. Goldthwait: The low white-cell count, the low neutrophil percentage, the clumped mucin and low sugar difference can be held as arguments against infection with a specific bacterial organism, although the clinical and x-ray findings could conceivably be consistent.

I should think benign tumors of the joint would not produce diffuse x-ray changes early in the course and the localized changes in the femoral neck later. One would have to consider, in addition to such entities as fibroma, myxoma and chondroma, a villonodular synovitis although this last is questionably neoplastic. The low red-cell count of 2250 per cubic millimeter in the joint fluid would be against tumor in the joint itself and particularly against villonodular synovitis.

One always has to consider rheumatoid arthritis, which we are learning can present all kinds of bizarre pictures, but such a diagnosis without the additional evidence of a large biopsy of both the bone lesion and the synovia should not be made.

I do not know what the child had. I have presented evidence against a good many things. The chief problem is that the joint disease and the bone lesion were too far apart to explain easily under one diagnosis.

I am inclined to vacillate between eosinophilic granuloma or osteoid osteoma in the femoral neck and an infectious process such as tuberculosis or a low-grade *Escherichia coli* infection in the joint. I should favor the former.

Dr. Castleman: That is, you would choose either an osteoid osteoma or an eosinophilic granuloma.

Dr. Goldthwait: Yes.

Dr. Castleman: Dr. Calkins, you saw this patient; have you any comment?

Dr. Calkins: I saw this patient with Dr. Morten Smith-Petersen and we agreed that exploration was in order. I was not as impressed with the lesion in the bone as Dr. Wang, Dr. Goldthwait and Dr. Smith-Petersen were although I had not seen the stereoscopic films. I believed that the most likely diagnosis was rheumatoid arthritis. The lack of other joint involvement and of constitutional symptoms was against this possibility but by no means ruled it out. The elevated sedimentation rate and fever during the second admission were consistent with this diagnosis. Dr. Smith-Petersen's thoughts ran more along the line of Dr. Goldthwait's. At the beginning of the operation, when we obtained the large amount of synovial fluid and observed that the synovia was very much thickened and red, I was beginning to be quite pleased with my diagnostic acumen. Dr. Smith-Petersen persevered, however, with the results that you will hear.

Clinical Diagnosis

?Rheumatoid arthritis.
?Osteoid osteoma.

Dr. Joel C. Goldthwait's Diagnosis

?Eosinophilic granuloma.
?Osteoid osteoma.

Anatomical Diagnoses

Osteoid osteoma of neck of femur.
Chronic synovitis of hip.

Pathological Discussion

Dr. Castleman: At the time of operation the surgeons first aspirated synovial fluid and looked at the synovia. There was a red pannus-like effect over part of the joint, which is what one ordinarily sees in rheumatoid arthritis in the active stage. As Dr. Calkins stated, most of the observers of the opened joint were satisfied that it was rheumatoid arthritis. The surgeons, however, decided to find out what the lesion in the bone was. I shall read a portion of the operative note:

> The capsule opening was then extended toward the neck of the femur, and as the base of the neck was ap-

proached it was noted that the bone was soft and that there was a cortical defect approximately 1.5 cm. in diameter. A needle was placed in this and x-ray films taken, and it was shown that this area represented the osteolytic area in the base of the femoral neck. A small osteotome was used for complete osteotomy around the margins of this lytic area, and the soft bone was excised in toto. A small curette was then used to scrape against the firm central bone, and a very soft, mushy area was found anteriorly approximately 0.25 cm. in diameter and another small area was noted somewhat lateral to the osteolytic area. Curettage was carried down to firm, cancellous central bone. The soft tissues were then allowed to fall back into place, and the wound closed in layers.

Microscopically, the area of rarefaction was a characteristic nidus of osteoid osteoma. The bone around the nidus was not as dense as it usually is in an osteoid osteoma, but there is no question in my mind that this was one. When we examined the synovia we found an inflammatory reaction with all types of cells and collections of lymphocytes among the synovial cells — a picture consistent with rheumatoid arthritis. It has been asserted by some pathologists that this type of inflammation in the synovia is pathognomonic of rheumatoid arthritis; however, we have seen sufficient cases now to realize that this may indicate a nonspecific inflammation and does not necessarily mean rheumatoid arthritis. In 1951 Mary Sherman[1] reported a series of 8 cases of various types of bone lesions that stimulated a reaction in the neighboring synovia, some of which were indistinguishable from rheumatoid arthritis. She referred to an earlier paper of hers describing 2 cases of osteoid osteoma[2] — 1 in exactly the same location as that in the child under discussion — that produced the same synovial reaction in the hip joint. As soon as the osteoid osteoma was removed, the pain disappeared, and later the synovial reaction disappeared.

Dr. Smith-Petersen told me that the day after the operation the patient voluntarily said that her hip was sore but the pain that had kept her awake for months had completely gone. This is the characteristic story after removal of an osteoid osteoma. When seen two months postoperatively she had full range of motion of the hip.

Osteoid osteoma is quite common in children from ten to twenty years of age. It produces pain very often at night, as in this child, and may be present for a long period. In the early stage the nidus may not be visible. It may take a while for the full-blown lesion to appear. As soon as it is removed, the pain is cured dramatically.

DR. CALKINS: Dr. Smith-Petersen pointed out that pain at night was against rheumatoid arthritis.

DR. CASTLEMAN: Many rheumatologists and pathologists have emphasized the characteristic appearance of rheumatoid arthritis; as Dr. Sherman has emphasized, one should be cautious about labeling a lesion rheumatoid arthritis merely on the basis of a lymphocytic infiltration of the synovia.

REFERENCES

1. Sherman, M. S. Non-specificity of synovial reactions. *Bull. Hosp. Joint Dis.* **12**:110-125, 1951.
2. *Idem.* Osteoid osteoma associated with changes in adjacent joints: report of two cases. *J. Bone & Joint Surg.* **29**:483-490, 1947.

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PROPHYLACTIC ANTIBIOTICS IN MEASLES

MUCH has been written in recent years about the role that the excessive use of antibiotics has played in establishing an antibiotic-resistant flora in the nasopharynx of the patients and personnel of the hospital, in infections of surgical wounds and in other nosocomial infections. In particular, the increasing frequency, in hospitals, of pathogenic staphylococci that are resistant to penicillin and to most of the other widely used antibiotics has received considerable attention recently, and the increasing number of serious infections with such antibiotic-resistant staphylococci is causing grave concern. Nevertheless, too many physicians and surgeons are still using antibiotics routinely as prophylactic agents in many conditions in which complicating bacterial infections may be expected or may be serious.

The efficacy of such prophylactic uses of antimicrobial agents has not been adequately assessed in most conditions in which they are employed, nor have the potential dangers of such uses received adequate attention. Yet this problem requires not only carefully controlled study but also review from time to time because of the changing bacterial interrelations resulting from the many therapeutic and prophylactic applications of these agents.

Comment was recently made in these columns* on the failure of antibiotics, used singly or in various combinations, to affect favorably the pathogenic bacterial flora in the trachea of tracheotomized patients with poliomyelitis. The prophylactic use of these agents in this condition failed not only to prevent the implantation of pathogenic organisms into previously sterile tracheas but also to cut down or to produce any favorable change in the bacterial flora in the tracheas that were already infected.

Elsewhere in this issue of the *Journal* Weinstein has critically reviewed the results of the use of antimicrobial agents for the prevention of the secondary bacterial complications of measles. This report from the Haynes Memorial, Massachusetts Memorial Hospitals, is of particular interest because the analysis includes not only patients who were treated during their hospital stay but also those who received the chemotherapeutic agents at home before admission to the hospital. In both groups bacterial complications were about twice as frequent in the patients who received antimicrobial agents prophylactically as they were in those who were not given such treatment. The data presented in Weinstein's report suggest not only that the antimicrobial agents failed to prevent serious bacterial complications but that their use was actually associated with an increased risk of such complications.

These results re-emphasize the need for critical review of the routine prophylactic use of antibiotics in

*Editorial. Antibiotics as prophylactic agents. *New Eng. J. Med.* **252**: 872, 1955.

simple nonbacterial infections — notably, the common cold — and influenza, and indeed in many other situations in which such prophylaxis is frequently advocated.

REGARDING CERTIFIED MILK

A RECENT report of the secretary of the Medical Milk Commission of Boston, Incorporated, reveals a number of interesting trends in the production of this unique food and beverage. Whereas a quarter of a century ago the Boston Commission approved and certified at least 9 farms the number today is 2 and had for some time been only 3; the most recent producer to abandon certification two or three years ago was the Walker-Gordon Farm at Charles River Village. Walker-Gordon having been for over fifty years the name most commonly associated with the production of certified milk, one can only reflect philosophically on those changes in the times and customs that are associated with progress.

Furthermore, although the number of milking cows at these 2 farms is the greatest it has been for several years, the amount of certified whole milk sold has fallen off about 20 per cent in only twelve months; the sales that make up the difference have been those of skimmed milk made from certified milk. Certified milk is thus changing its function to a low-calorie food for fat folk from a de luxe product for infants and children. Whether the mature watchers of the waistline require the same quality features is debatable, especially in view of the high standards required of all grades of milk sold in the local area.

In addition to the painstaking technic required in the production of milk marketed under its seal the Boston Commission requires that it shall be pasteurized. This is considered in various other parts of the country to be painting the lily; according to certain local prejudices pasteurization should be the *sine qua non*, and the special requirements of certification are taken to represent the extra refinement. The painting, however, is artistically done. The standards generally required for certification include bacteria counts of not over 5000 colonies in the raw milk and 100 in certified milk pasteurized; the average actual counts for the two farms certified by the local commission have been 550 for the raw milk and 4 and 6, respectively, for the same milk when pasteurized. The suggestion recently made at the annual meeting of the American Association of Medical Milk Commissions that standards in general be elevated by a lowering of the permissible bacterial counts was graciously considered but declined.

Certification, in various parts of the country, is still employed, as it was fifty years ago, to make a raw milk as safe as possible.

THE WASHINGTONIAN HOSPITAL: A NEW PHASE

FOR nearly a hundred years the Washingtonian Hospital in Boston — the oldest American institution devoted exclusively to the treatment of chronic alcoholism — has been a haven for people suffering loss of health and self-respect because of uncontrollable drinking. For many years, a grimy and depressing brick building in Boston's South End served inadequately as a facility for treating the addicts.

Early this year, the Hospital moved into excellent headquarters at 39 Morton Street, Jamaica Plain. Renovation of the building on the new site, with necessary adaptations, has resulted in a first-class center for the treatment of this disease.

Expansion into modern hospital facilities— regardless of the kind of service — is an occasion for celebration. But expansion means not only better facilities and better service — it means greater financial liability. Needed by January, 1956, is $211,000 to pay for the new building, exclusive of a sizable sum already spent for renovation and modification of the property.

The trustees of the Washingtonian Hospital recently started a special gift campaign to provide this money. It is hoped that the response will place the institution in a strong position to carry on the fine work it has been doing in the rehabilitation of alcohol addicts.

By invitation we have recently examined, at Joy's Building in this city, an invention that must prove exceedingly serviceable to active medical practitioners, and we have no doubt a description of it would prove interesting to them. In the first place, there is a kind of clock movement — a coiled spring, a ratchet wheel and a small bell — which may be screwed to the wall in a sleeping-chamber, at the head of the bed or over a dressing table, and a wire leads from it to the door-bell. On retiring, it is wound up, and the alarm wire is simply hooked on. When the bell-pull is drawn, at the front door, the alarm bell begins to strike rapidly, and in the same moment a match lights a spirit lamp. . .

Boston M. & S. J., *Oct. 25, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

ECLAMPSIA FOLLOWED BY CEREBRAL HEMORRHAGE

A twenty-seven-year-old gravida I, para 0, died two weeks before term because of a cerebral hemorrhage that followed two eclamptic convulsions.

The patient, who was known to have epilepsy, had been in control of this disease on sodium diphenylhydantoin (Dilantin) and phenobarbital for many years. She and her husband lived with the patient's mother in a home that also housed the mother's other 12 children. Perhaps for this reason, abnormal findings such as edema and hypertension were heavily discounted by the mother, who upbraided the patient for laziness whenever she went to bed on doctor's orders. Furthermore, a sister was a registered nurse and freely offered to take care of her at home when hospitalization was recommended. These factors produced an extremely unco-operative patient from the physician's point of view.

The first prenatal visit was in the fifth month, when all findings were normal except for a total gain of 7.7 kg. (17 pounds) in weight. She broke the next appointment but showed up in the seventh month with still further weight gain without hypertension or albuminuria. However, at the beginning of the eighth month, the blood pressure was 150 systolic, 100 diastolic, and the urine gave a ++++ test for albumin. Hospitalization was advised but refused, and the patient was therefore put to bed at home on a salt-free diet, ammonium chloride and increasing doses of phenobarbital. The physician questions how closely this regimen was followed. He visited the patient faithfully at home every day for five days and had the sister give intramuscular injections of 50 per cent magnesium sulfate, 2 cc. twice daily. This resulted in some weight loss, but albuminuria and blood-pressure elevations continued. Repeatedly, in the next sixteen days, hospitalization was advised but refused. During this interval the physician made frequent house calls, finding the blood pressure as high as 160 systolic, 100 diastolic, but he made no further urinalyses. For the next week he made daily telephone inquiries about headache and other symptoms, with negative reports. Eleven days after his last house call, he again examined the patient, finding a blood pressure of 200 systolic, 150 diastolic. She was now complaining of severe headache as well as vomiting and diarrhea. The last two symptoms were shared by the rest of this large household, who had "intestinal flu." Under these circumstances the patient agreed to enter the hospital on the following morning. However, on the next morning the physician found that she had been up most of the night with vomiting and diarrhea and was in an apparently postconvulsive, comatose state. None of the rest of the household had observed the convulsion. She was transferred by ambulance to the hospital, where the blood pressure was 206 systolic, 138 diastolic, and the pulse 120; vomiting was constant, and she complained bitterly of headache. Two hours later spontaneous labor began, the treatment in the meantime having been 1 gm. of magnesium sulfate, 0.3 gm. of phenobarbital and 1 ampoule of vitamin B intramuscularly. About three hours after admission, the patient experienced a convulsion, which lasted for three and a half minutes, after which she remained in coma, and it was noted that she now failed to move the arm and leg on the right side but moved her other arm and leg a great deal. Further doses of amobarbital (Amytal Sodium) and phenobarbital were given, but no more magnesium sulfate, and her condition gradually deteriorated. Labor stopped, and the next morning at 5:20 a.m. she died after the pulse and temperature had risen. During the short labor, which lasted about three hours, the cervix had become as much as 4 cm. dilated but did not go beyond this as proved by autopsy. Autopsy also showed the typical findings of eclampsia as well as a left frontal cerebral hemorrhage.

This was classified as a preventable death, the avoidable factor being inadequate prenatal care. Well aware of the circumstances, the Committee assigned responsibility very heavily to the patient and her family. However, it is of the opinion that a physician must decline responsibility for such a patient and advise her to seek care elsewhere if she will not follow orders. This is particularly true in so hazardous a state as pre-eclampsia.

As far as treatment after hospitalization is concerned there is little to add except that much larger doses of magnesium sulfate should have been used, with at least a small possibility of avoiding the terminal cerebral hemorrhage. With convulsions under control urgent efforts to empty the uterus were called for, and it is entirely possible that she might have survived.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATHS

FLYNN — James L. Flynn, M.D., of Boston, died on September 26. He was in his forty-fifth year.

Dr. Flynn received his degree from Georgetown University School of Medicine in 1939.

He is survived by his widow, a son and a daughter.

MURPHY — Lawrence Murphy, M.D., of Newburyport, died on September 23. He was in his sixty-first year.

Dr. Murphy received his degree from the St. Louis College of Physicians and Surgeons. He was a member of the staffs of the Anna Jaques and George W. Worcester Memorial hospitals.

He is survived by two brothers.

WILLIAMS — John T. Williams, M.D., of Boston, died on September 8. He was in his seventy-third year.

Dr. Williams received his degree from Harvard Medical School in 1904. He was formerly chief of gynecology and obstetrics at Boston City Hospital and was a fellow of the American Medical Association and the American College of Surgeons.

He is survived by his widow, a daughter and two grandchildren.

NOTICES

HARTFORD MEDICAL SOCIETY

The program for the fall and early-winter lecture series of the Hartford Medical Society is as follows:

November 7. Immunohematology in Clinical Practice. Dr. William Dameshek.

November 21. The Diagnosis and Treatment of Tumors of the Soft Somatic Tissues. Dr. George Pack.

December 5. Poliomyelitis — 1955. Dr. Louis Weinstein.

January 16, 1956. Panel: Medical and surgical aspects of peptic ulcer. Drs. Richard Warren, Thomas Machella and Benjamin White.

The lectures will be held in the Hunt Memorial Building, Hartford, Connecticut, at 8:30 p.m. All physicians are cordially invited to attend.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the auditorium of the Jimmy Fund Building, Children's Medical Center, 35 Binney Street, Boston, on November 8 at 8 p.m.

This meeting will be devoted to a symposium on poliomyelitis.

SOCIETY MEETINGS AND CONFERENCES

October 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

October 24–27. Consultation Clinics for Crippled Children in Massachusetts. Page 575, issue of September 29.

October 24–29. American College of Gastroenterology. Page 488, issue of September 15.

October 24, November 7 and December 5, 1955, and January 16, February 6, March 5 and April 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

October 25. New England Diabetes Association. Page 667, issue of October 13.

October 25 and November 1. Boston City Hospital House Officers' Association. Page 577, issue of September 29.

October 26. New England Pediatric Society. Page 623, issue of October 6.

October 26 and November 30, 1955, and January 25, March 21 and April 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

October 26, 1955–May 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

October 27. Massachusetts Trudeau Society. Page 667, issue of October 13.

October 27. New York Diabetes Association. Page 667, issue of October 13.

October 27 and 28. New York Medical Conference. Page 394, issue of September 1.

October 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.

November 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

November 2. New England Conference on Allergy and Related Subjects. Page 667, issue of October 13.

November 2–5. American Society of Tropical Medicine and Hygiene. Page 624, issue of October 6.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 7, 21 and December 5, 1955 and January 16, 1956. Hartford Medical Society. Notice above.

November 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

November 8. Harvard Medical Society. Notice above.

November 10–12. American College of Cardiology. Page 394, issue of September 1.

November 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

November 14 and 18. American Public Health Association. Page 578, issue of September 29.

November 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

November 17 and December 15. Arthritis Study Unit. Page 668, issue of October 13.

November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

November 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

November 28–December 2. Interim Session of the American Medical Association, Boston.

December 5–14, 1955, and January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

December 7, 1955, and January 25, February 29, March 21 and April 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

December 14, 1955, and February 15, March 28 and April 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

March 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

May 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 27

THURSDAY, OCTOBER 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m.–12:00 m. Thoracic Conference. Unrestricted Discussion of the High Diaphragm. Dr. James B. Dealy. Amphitheater, Peter Bent Brigham Hospital.
*12:00–1:00 p.m. The Surgery of Peripheral Arteriosclerosis. Dr. Richard Warren. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
8:00–10:00 p.m. Massachusetts Trudeau Society. Auditorium, Peter Bent Brigham Hospital.

FRIDAY, OCTOBER 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*7:30–9:30 p.m. Postgraduate Medical Institute. Treatment of Kidney Disorders in Adults. Drs. Aisner and Relman. Holyoke Soldiers' Home, Holyoke.

SATURDAY, OCTOBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, OCTOBER 31

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Lecture and Clinic. Gout. Dr. Siegfried J. Thannhauser. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

(Concluded on page xxxv)

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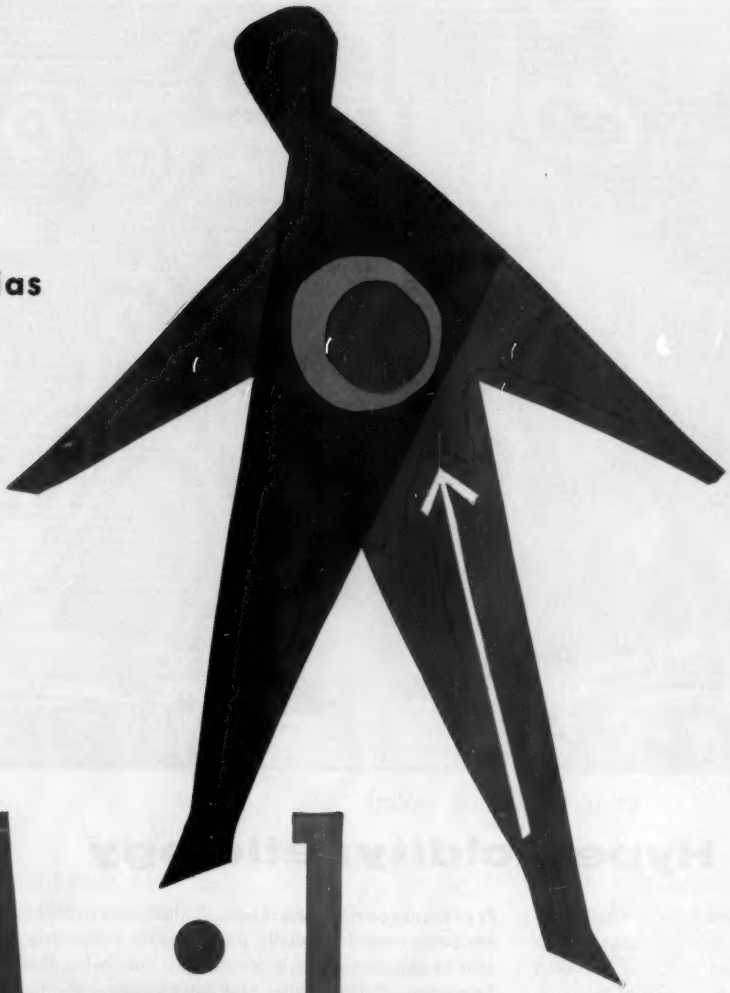

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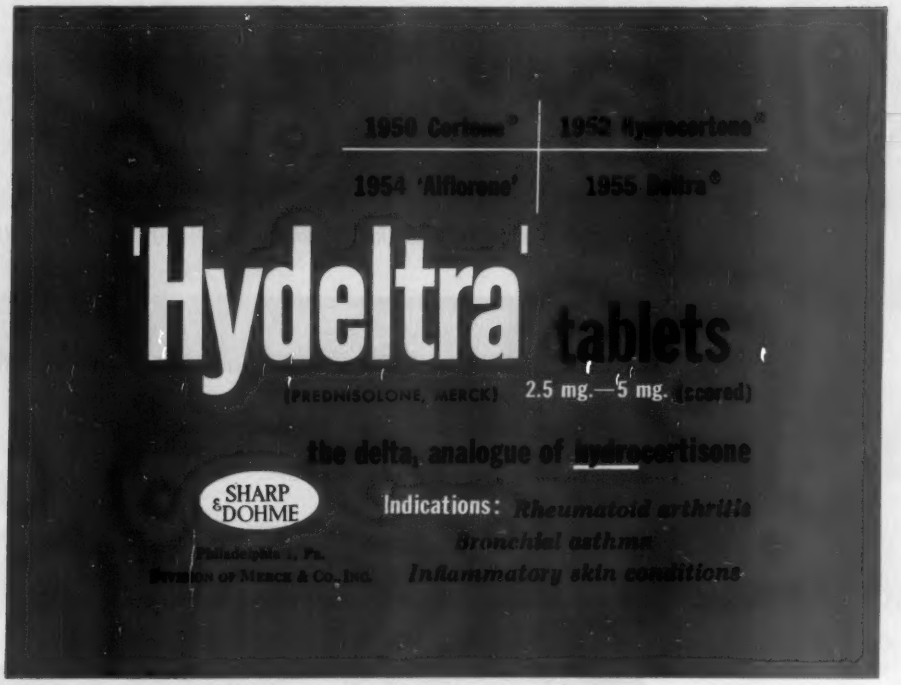

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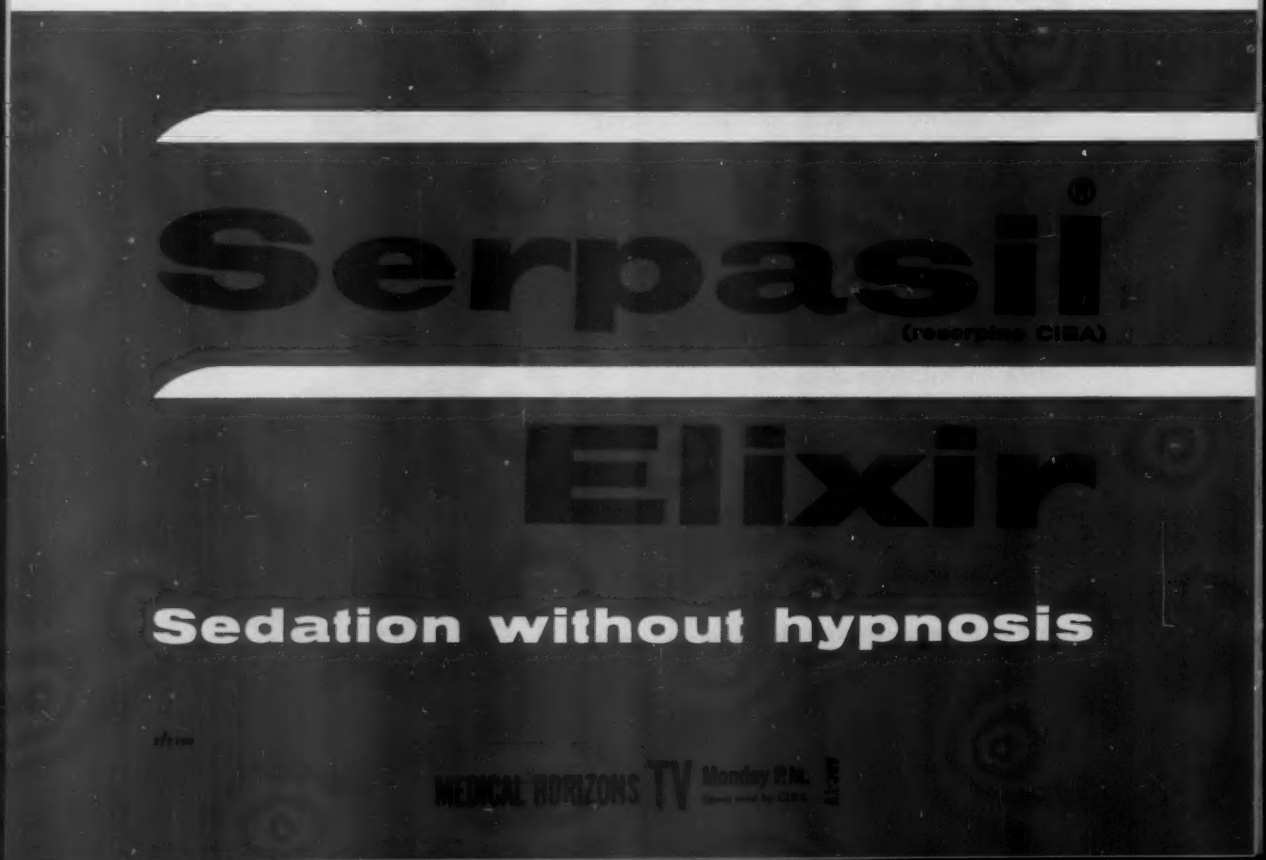

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(Additional advertisements on page xxviii)

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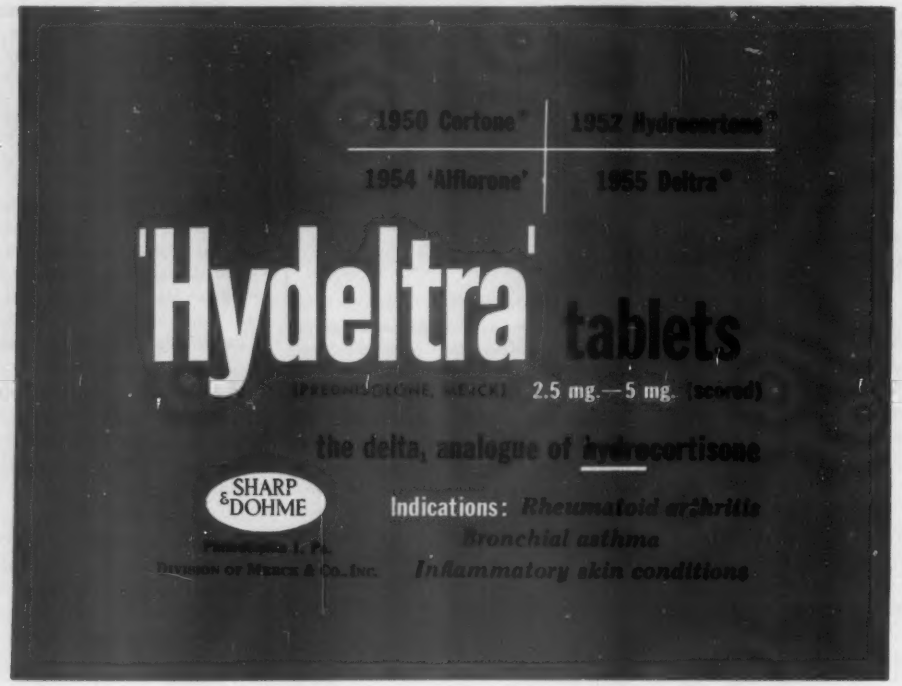

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(Additional advertisements on pages xxvi and xxvii)

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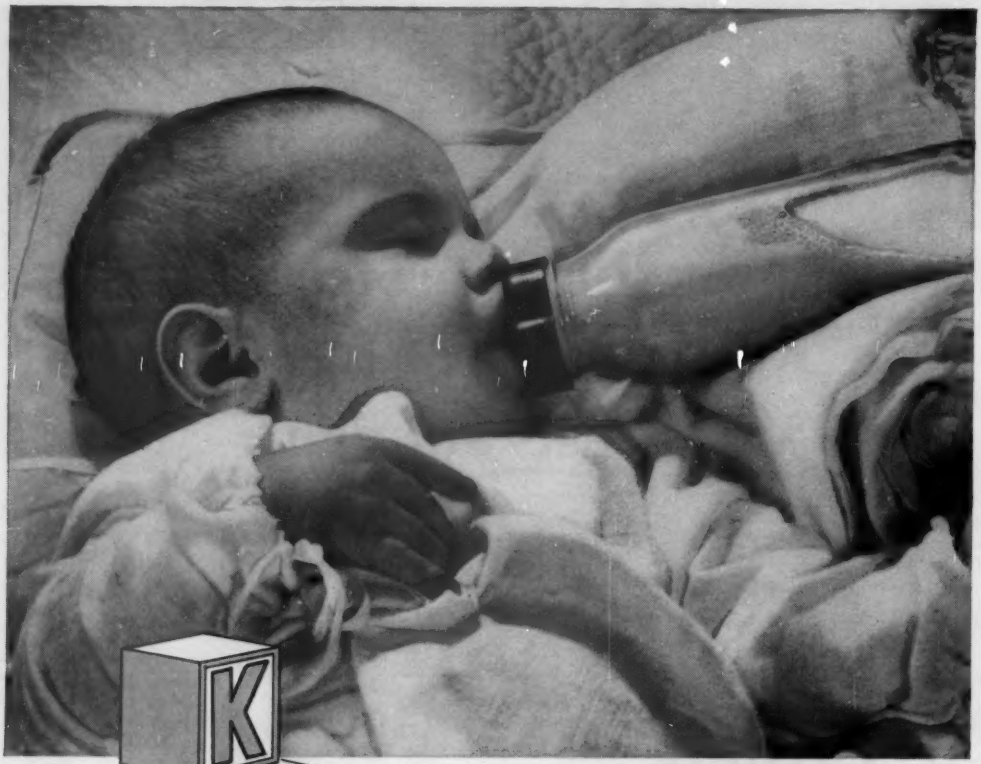

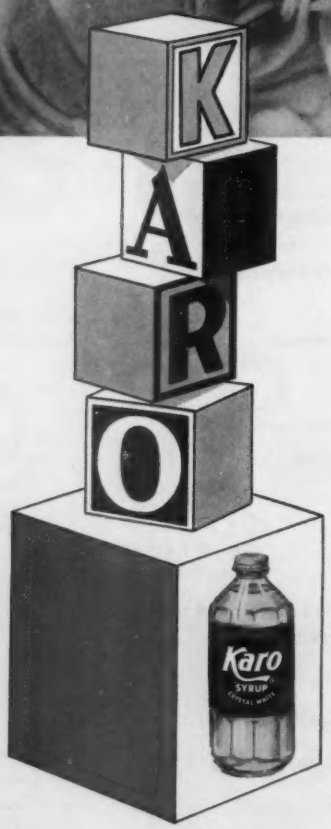

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1. Parish, F. A.: M. Times 82:917, 1954.
2. Menger, H. C.: New York J. Med. 55:812, 1955.

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1. Bender, T. J. Jr.: at Mtg. Med. Assoc. St. Alabama, Mobile, 1954.
2. Jessup, R., Murray, R. J. and Rossi, A.: Amer. Pract. & Dig. of Treatment, 5:792, 1954.

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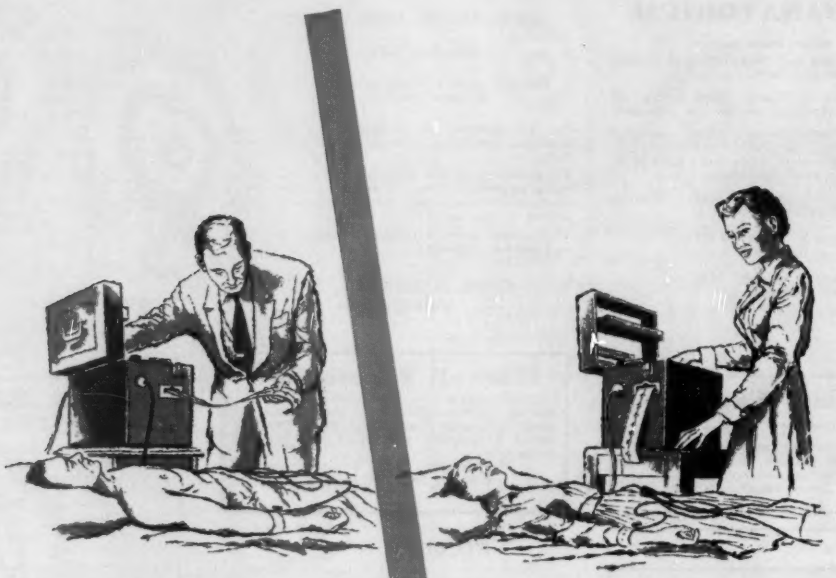

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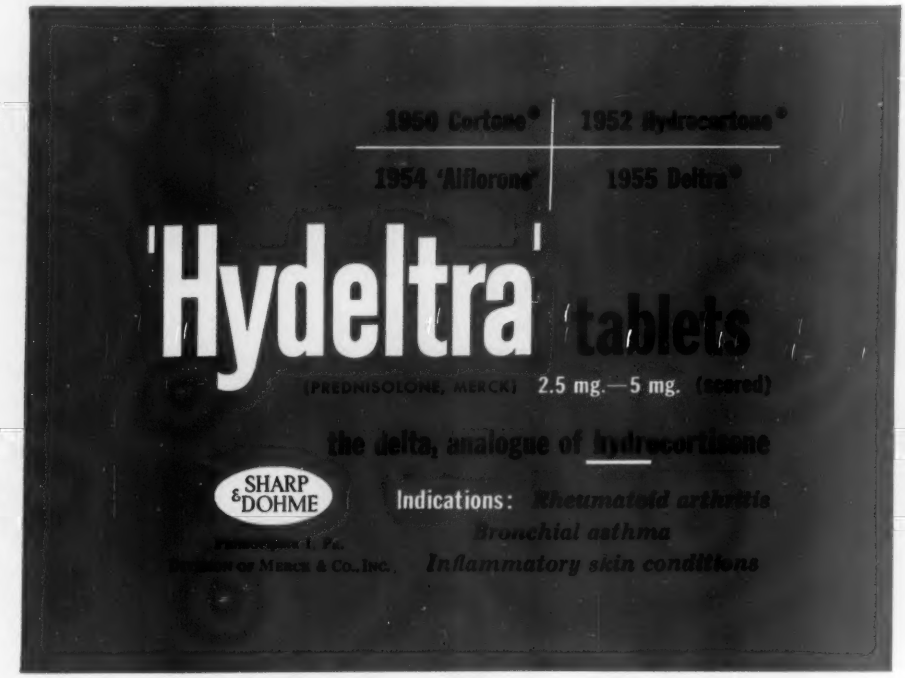

(Concluded from page 708)

*4:00–5:30 p.m. Anesthesiology Conference. Mortality and Morbidity. Dr. Orr. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, NOVEMBER 1

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Drs. Patterson, MacMahon and guest. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten and staff. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. A New Group of Rhinoenteric Viruses. Dr. Albert B. Sabin. New Cheever Amphitheater, Boston City Hospital.

WEDNESDAY, NOVEMBER 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Communication in an Organization. Dean, Erwin H. Schell. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–1:00 p.m. Postgraduate Medical Institute. Jaundice and Hepatitis. Drs. Culver and McDermott, Jr. St. John's Hospital, Lowell.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*2:00–4:00 p.m. Postgraduate Medical Institute. Rehabilitation of Children with Paralytic Polio. Drs. Ferris and Norton. Lemuel Shattuck Hospital, Jamaica Plain.
*2:00–4:00 p.m. Postgraduate Medical Institute. Anemia. Dr. William Dameshek. Norfolk County Hospital, Braintree.
*2:00–4:00 p.m. Postgraduate Medical Institute. Postpartum Complications. Drs. Ferrone and Grogan. St. Luke's Hospital, New Bedford.
*3:00–5:00 p.m. New England Conference on Allergy and Related Subjects. New England Medical Center, 37 Bennet Street, Boston.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Medical Institute. Abnormal Uterine Bleeding. Drs. Horne, Jr., and Kistner. St. Luke's Hospital, Pittsfield.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.
*8:30 p.m. New England Conference on Allergy and Related Subjects. Sheraton Plaza, Boston.

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